



Toxoplasmosis: Targeting neurotransmitter systems in psychiatric disorders

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Abstract

The most common form of the disease caused by *Toxoplasma gondii* (*T. gondii*) is latent toxoplasmosis due to the formation of tissue cysts in various organs, such as the brain. Latent toxoplasmosis is probably a risk factor in the development of some neuropsychiatric disorders. Behavioral changes after infection are caused by the host immune response, manipulation by the parasite, central nervous system (CNS) inflammation, as well as changes in hormonal and neuromodulator relationships. The present review focused on the exact mechanisms of *T. gondii* effect on the alteration of behavior and neurotransmitter levels, their catabolites and metabolites, as well as the interaction between immune responses and this parasite in the etiopathogenesis of psychiatric disorders. The dysfunction of neurotransmitters in the neural transmission is associated with several neuropsychiatric disorders. However, further intensive studies are required to determine the effect of this parasite on altering the level of neurotransmitters and the role of neurotransmitters in the etiology of host behavioral changes.

Keyword *Toxoplasma gondii*. Neurotransmitter. Psychiatric disorders. Cytokine

Abbreviations

CNS	Central nervous system	TH	Tyrosine hydroxylase
DALYs	Disability-adjusted life years	D2R	Dopamine receptor D ₂
HIV	Human immunodeficiency virus	TNF	Tumor necrosis factor
<i>T. gondii</i>	<i>Toxoplasma gondii</i>	NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
IgG	Immunoglobulin G	IL-1β	Interleukin 1 beta
MDD	Major depression disorder	GABA	Gamma-aminobutyric acid
SZ	Schizophrenia	NO	Nitric oxide
BD	Bipolar disorder	DR	Dopamine receptors
OCD	Obsessive–compulsive disorder	AAH	Aromatic acid hydroxylase genes
AD	Alzheimer's disease	IFN-γ	Interferon-gamma
PD	Parkinson's disease	NK	Natural killer
ADHD	Attention-deficit hyperactivity disorder	GTP-CH1	Guanosine triphosphate cyclohydrolase 1
		BH4	Tetrahydrobiopterin
		DCs	Dendritic cells
		TLR	Toll-like receptor
		IDO	Indoleamine 2,3-dioxygenase
		KA	Kynurenic acid
		QA	Quinolinic acid
		NMDA	N-methyl-D-aspartate
		MAPK	Mitogen-activated protein kinases
		MAOA	Monoamine oxidase A
		MeHg	Methylmercury
		Th	T helper
		EAATs	Excitatory amino acid transporters
		GAD67	Glutamic acid decarboxylase 67

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CCL5	CC chemokine ligand 5
CXCL9	CXC chemokine ligand 9
CXCL10	CXC chemokine ligand 10
WFS1	Wolfram syndrome 1
MePD	Poster-dorsal medial amygdala
AVP	Arginine vasopressin
eNOS	endothelial nitric oxide synthase
nNOS	Neuronal nitric oxide synthase
iNOS	Inducible nitric oxide synthase

Introduction

Mental and behavioral disorders are considered major public health problems. These disorders affect 10–16% of the world population every year (Fekadu et al. 2010; Wang et al. 2006). One of the major causes of disability and mortality around the world is neurological disorders. Population growth and aging population significantly increase the burden of neurological disorders in the past 25 years worldwide. Generally, the rate of mortalities and number of disability-adjusted life years (DALYs) resulted from neurological disorders increased by 36.7% and 7.4% within 1990 and 2015 (Feigin et al. 2017). The results of a systematic analysis on the global burden of mental diseases showed that neurological disorders were responsible for 10.2% of global DALYs (i.e., 250.7 million) and 16.8% of global mortalities (i.e., 9.4 million) (Feigin et al. 2017). The causes of mental illnesses are often unknown; however, biological, psychological, and environmental factors play a role in causing psychiatric disorders individually or in combination. Among the biological factors, genetic factors, traumatic brain injury, noninfectious diseases, such as epilepsy, birth trauma, and oxygen starvation are important. Likewise, the influence of gut flora on brain function has shown a two-way interaction between the gut and brain that affects an individual's mood, motivation, decision-making, and cognitive abilities (Tyebji et al. 2019). Therefore, microorganisms that cause gastrointestinal diseases may affect mental health (Bolton and Robertson 2016). In addition, infectious diseases can be among the causes of mental disorders. Infectious diseases, such as malaria, syphilis, Legionnaire's disease, diphtheria, typhoid, herpes, and human immunodeficiency virus (HIV), cause psychiatric symptoms (Bolton and Robertson 2016). One of these diseases is toxoplasmosis, which is associated with altered neurological function (Tedford and McConkey 2017).

Toxoplasma gondii (*T. gondii*) is an obligate intracellular protozoan infecting almost all warm-blooded animals, including mammalian and several species of birds (as intermediate hosts), and its definitive host is a cat family (i.e., Felidae) (Fuglewicz et al. 2017; McConkey et al. 2013). *T. gondii* possesses a complex life cycle, which is composed of the three infectious phases: a sexually replicative stage

in definitive hosts, an asexual replicative stage in the intermediate hosts, and an exogenous stage (oocysts containing sporozoites) (Montoya and Liesenfeld 2004). During these stages, the parasite is observed in three infectious forms, including tachyzoite present in body fluids during acute infection, bradyzoite contained within tissue cysts during chronic infection, and oocyst (excreted from the feces of cats) (Tenter et al. 2000). The seroprevalence of *T. gondii* infection measured by specific anti-*Toxoplasma* immunoglobulin G (IgG) antibodies widely varies within the range of 1–100% worldwide. Variations in prevalence depend on the environmental and socioeconomic conditions, including climatic and geographic factors, hygiene standards, feeding and cultural habits, as well as professions (Dubey 1998; Dubey and Beattie 1988; Furtado et al. 2011; Tenter et al. 2000). The lowest seroprevalence (about 1%) was reported in some countries in the Far East, and the highest seroprevalence (less than 90%) was reported in some parts of European and South American countries (Flegr et al. 2014a). Different factors, such as the strain and virulence of parasite, number of ingested organisms, immunity status, gender, and genetic background of the host, are crucially important in the progress of infection (Montoya and Liesenfeld 2004). The most important routes of infection are the consumption of oocysts present in the environment, drinking contaminated water, ingestion of tissue cysts in raw or undercooked meat of intermediate hosts, organ transplantation, and transplacental transmission of tachyzoites (Carruthers and Suzuki 2007; da Silva and Langoni 2009; Flegr et al. 2014b; Tedford and McConkey 2017). It is believed that if most healthy individuals are infected with this parasite, they are generally asymptomatic or show a subclinical course with minor symptoms (Montoya and Liesenfeld 2004). Primary infection in pregnant women can be transmitted to the fetus and lead to spontaneous abortion or childbirth (Flegr et al. 2014a). Toxoplasmosis can cause a variety of life-threatening clinical signs in cases of congenital infection which can result in a wide diversity of manifestations in neonates, such as hydrocephalus, microcephaly, and retinochoroiditis, or immunocompromised patients, including HIV-positive individuals, cancer patients, and transplant recipients (Ahmadpour et al. 2014; Jones et al. 2003). In the aforementioned subjects, acute infection or reactivation of latent toxoplasmosis might develop severe clinical complications with poor prognoses, such as toxoplasmic encephalitis, brain abscess, pneumonitis, myocarditis, and chorioretinitis (Abedalthagafi et al. 2009; Ahmadpour et al. 2014; Sutherland et al. 2015). Some diseases, such as ocular toxoplasmosis, occur both in immunocompetent and immunocompromised individuals (Furtado et al. 2011; Klaren and Kijlstra 2002; Montoya and Liesenfeld 2004). Parasite through the Trojan horse mechanism can migrate to the immunoprivileged organs, eyes, testes, and especially brain (Jaroslav Flegr 2015). This

parasite possibly enters the brain as early as 7 days after the infection (Konradt et al. 2016). Lesions in the brain by interfering with the functions of the brain in the region around the lesion through paracrine secretions or mass effects can appear as behavioral symptoms (Mentzer et al. 2012). The results of a study carried out on mice showed that the cyst cannot directly cause behavioral changes by disrupting the surrounding tissue (Gatkowska et al. 2012). The possible ability of the parasite to change human behavior can be influenced by the factors, such as one's genetic susceptibility, time of the person's life at which the infection occurs, severity of the initial acute infection, ingestion stage of the parasite, as well as the exact number and location of parasitic cysts in the brain at the chronic stage of infection (Henriquez et al. 2009; McConkey et al. 2013).

Flegr *et al.* in 2014 studied the seroprevalence of latent toxoplasmosis and its relationship with mortality and disability rates of specific diseases in 88 countries around the world. The analyses revealed that DALYs associated with 23 of the 128 analyzed diseases correlated with the prevalence of toxoplasmosis (18 positive and 5 negative), and the other 12 cases showed a positive trend (Flegr et al. 2014a). In addition, the probable association between *T. gondii* infection and mental disorders has been investigated in several systematic reviews and meta-analyses. The most common of these disorders are major depression disorder (MDD) (Nayeri Chegeni, et al. 2019a; Sutterland et al. 2015), schizophrenia (SZ) (Sutterland et al. 2015; E. F. Torrey et al. 2007), bipolar disorder (BD) (de Barros et al. 2017; Sutterland et al. 2015), addiction (Sutterland et al. 2015), obsessive–compulsive disorder (OCD) (Nayeri Chegeni et al. 2019b), Alzheimer's disease (AD) (Bayani et al. 2019; Nayeri Chegeni, et al. 2019c), Parkinson's disease (PD) (Bayani et al. 2019), attention-deficit hyperactivity disorder (ADHD) (Nayeri et al. 2020a), epilepsy (Ngoungou et al. 2015; Sadeghi et al. 2019), suicide attempts (Sutterland et al. 2019; Amouei et al. 2020), traffic accidents (Gohardehi et al. 2018; Sutterland et al. 2019), autism (Nayeri et al. 2020b), and headache (Nayeri et al. 2020c). The results of these studies showed that chronic *T. gondii* infection is a factor associated with SZ, BD, OCD, AD, addiction, epilepsy, suicide attempts, autism, headache and traffic accidents but not with MDD, ADHD, and PD. *T. gondii* infection may also be associated with some other disorders, but further studies are needed to confirm these relationships. For example, a case–control study showed that chronic toxoplasmosis was not associated with sleepiness and sleep apnea syndrome severity in obese patients suspected of sleep apnea syndrome (Dard et al. 2020).

There are several mechanisms used by the parasite to cause the disease. The first mechanism is the alteration of different neurotransmitters pathways indicating that *T. gondii* has genes encoding proteins homologous to aromatic amino

acid tyrosine hydroxylase (TH) and dopamine receptor D₂ (D2R). The parasite also increases dopamine synthesis and tryptophan degradation and decreases serotonin synthesis (Henriquez et al. 2009). The second mechanism used by the parasite is the induction of the immune responses (Henriquez et al. 2009), and the third is the induction of endocannabinoids (Melamede 2009). Accordingly, different changes, such as anatomical, immunological, and pathological, as well as changes in neurotransmitter levels and gene expressions, may occur during the brain infection with *T. gondii*. Moreover, some of these changes may result in various neurological diseases (Abdoli et al. 2014). The ability of the parasite to influence neurotransmitter pathways is one of the most important mechanisms. Firstly, in the 1970s, Stibbs (Stibbs 1985) described changes in different neurotransmitter concentrations with *T. gondii* infection and reported a decrease in norepinephrine and serotonin synthesis, as well as increasing dopamine synthesis in the brain of infected mice with chronic infection. According to the above-mentioned content and importance of the role of neurotransmitters in causing mental disorders, the present study aimed to review the current state of knowledge regarding the role of neurotransmitters and increasing or decreasing their levels in the development of mental disorders. In addition, this study aimed to identify several gaps that can improve the diagnosis and treatment of mental health problems.

Neurotransmitter systems

The nervous system includes billions of specialized cells called neurons. Neurons are cells that establish chemical communication in the brain. A neuron has two ends (i.e., one axon and one dendrite). The normal functioning of the central and peripheral nervous system requires efficient communication between neurons (Patri 2019). Neurotransmitters are a diverse group of chemical compounds in the brain that serves as the mediator for the transmission of nerve impulses from the presynaptic site of one neuron to the postsynaptic site of another neuron via synapses (Leite et al. 2017). These neurotransmitters are stored in small packets called synaptic vesicles in axons (or presynaptic neurons) (Ayano 2016). The arrival of a nerve impulse or an action potential at the nerve terminal leads to the release of neurotransmitters (Patri 2019). The decreased release of neurotransmitters results from the loss of neurons and synapses leading to learning and memory problems (Parlog et al. 2015). The nuclear factor kappa light-chain enhancer of activated B cells (NF- κ B) pathway is an intracerebral inflammatory pathway activated in the brain of mice chronically infected with *T. gondii*. The overexpression of cytokines, such as tumor necrosis factor (TNF), interleukin 1 beta (IL-1 β), and Toll-like receptors, activated the NF- κ B pathway (Courtois

and Gilmore 2006; Wang et al. 2019), and the activation of this pathway may enhance the inflammatory response to the CNS injury. Excessive immune responses can induce neuronal apoptosis and lead to decreased synaptic density in the brain (Zhang et al. 2014). Substances that act as neurotransmitters can be classified into different groups as follows:

1. Amino acids: Glycine, glutamate, aspartic acid, and gamma-aminobutyric acid (GABA).
2. Amino acid-derived amines: Norepinephrine (noradrenaline), epinephrine (adrenaline), dopamine, serotonin (5-HT), and histamine.
3. Gasotransmitters: Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H₂S).
4. Peptides: Substance P and endorphins.
5. Purines: Adenosine triphosphate.
6. Others: Acetylcholine (Abg Abd Wahab et al. 2019; Mustafa et al. 2009; Patri 2019).

Neurotransmitters are divided into three groups of excitatory, inhibitory, and modulatory based on their effects on signal transmission (Tyebji et al. 2019). Amino acid neurotransmitters and amino acid-derived amines are inhibitory and excitatory (Patri 2019). Some neurotransmitters (e.g., glutamate, serotonin, acetylcholine, epinephrine, and norepinephrine) are excitatory; however, other neurotransmitters (e.g., glycine and GABA) are inhibitory (Abg Abd Wahab et al. 2019; Patri 2019). Unlike other neurotransmitters, dopamine can act as both inhibitory and excitatory depending on its position in the brain and which receptor it connects to (Nakamura et al. 2014). Amino acid neurotransmitters play a role in fast synaptic transmission; nevertheless, amino acid-derived amines are involved in slow synaptic transmission (Patri 2019). Out of the aforementioned groups of neurotransmitters, amino acids (i.e., glutamate and GABA), amino acid-derived amines (i.e., norepinephrine, epinephrine, dopamine, and serotonin), and others (i.e., acetylcholine and NO) are involved in the CNS infection by *T. gondii*. Therefore, this article reviewed the possible roles and mechanisms of these neurotransmitters in mental disorders caused by *T. gondii* infection (Fig. 1).

Dopamine

Dopamine (4-[2-aminoethyl] benzene-1,2-diol) is one of the most important catecholamine neurotransmitters in the mammalian CNS (Fig. 2). Dopamine is a chemical material released by one neuron to send signals to other neurons. Furthermore, dopamine is a chemical messenger and plays a key role in the functioning of the kidney, as well as hormonal and cardiovascular systems (van Staden and van Staden 2012). In 1910, dopamine was firstly synthesized

by George Barger and James Ewens (van Staden and van Staden 2012). In addition, the function of dopamine as a neurotransmitter was initially recognized in 1958 (van Staden and van Staden 2012). The cell bodies of the dopaminergic neurons are concentrated in several areas of the brain, including the ventral tegmental area, substantia nigra, and retrorubral field, and projected to the basal ganglia, limbic regions, olfactory bulbs, hippocampus, and cortex. The prefrontal cortex involved in planning, decision-making, problem-solving, and coordinating performance in humans is rich in dopamine (Diamond et al. 2004). Dopaminergic neurons appear in humans and rats early within 6–8 weeks of pregnancy and 10–15 days of gestation, respectively. The appearance of these neurons occurs later in males than that reported for females (Herlenius and Lagercrantz 2004). There are five known dopamine receptors (DR) (i.e., D₁, D₂, D₃, D₄, and D₅); however, D₁R and D₂R are two main types used by the brain (Herlenius and Lagercrantz 2004). The D₁R mediates excitatory signaling pathways; nonetheless, D₂R mediates inhibitory signaling pathways (Nakamura et al. 2014). Dopamine is involved in many brain circuits in the nervous systems associated with mediating motor control, emotional and cognitive aspects, arousal, reward, and feeding behavior (Abg Abd Wahab et al. 2019). The presence of dopamine neurotransmitter is necessary for the long-term regulation of brain functions (Tyebji et al. 2019). Dopamine is an important neurotransmitter that plays a role in the etiology of several human disorders, such as AD, PD, SZ, and depression (Davis et al. 1991). An increase in dopamine levels in the brains of the mice infected with *T. gondii* was described in 1985 (Stibbs 1985). Dopamine levels decrease in some psychiatric disorders and increase in others; for example, decreased dopamine levels are often observed in patients with SZ (Davis et al. 1991); however, the levels of this neurotransmitter increase in patients with MDD, AD, and PD (Wolfe et al. 1990). The concentration of dopamine increased in the acute phase of *T. gondii* infection in mice (Gatkowska et al. 2013). In addition, this increase in concentration was observed in the chronic stage, as well as the tissue and their surroundings (Prandovszky et al. 2011). On the other hand, since dopamine increases the number of *T. gondii* tachyzoites in cultured fibroblasts, it can be said that neurotransmitters may manipulate the parasite (Stibbs 1985). The antipsychotic dopamine-blocking agent haloperidol (i.e., a typical antipsychotic known dopamine D₂ antagonist) used in the treatment of SZ and other psychiatric disorders can inhibit the in vitro replication of *T. gondii* (Webster et al. 2006). The results of in vitro studies indicated that dopamine may play a variety of roles in the brain, including reproduction, chemotherapy, infection efficiency, and conversion of cyst stage to tachyzoite (Strobl et al. 2012). Tissue cysts have been identified throughout the brain, although there are a greater number of cysts

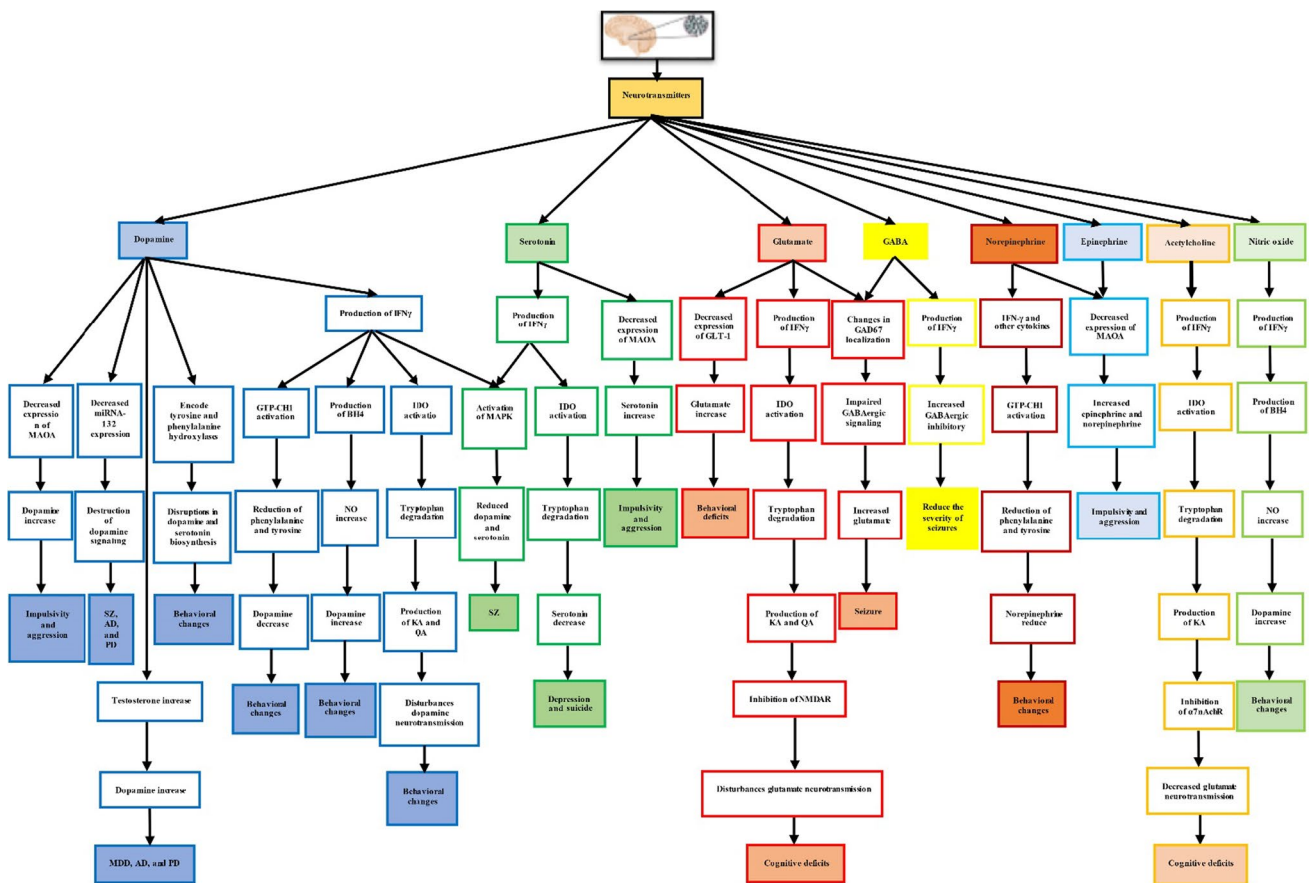


Fig. 1 Potential mechanisms utilized by *Toxoplasma gondii* to alter the level of neurotransmitters and intermediate host behavior

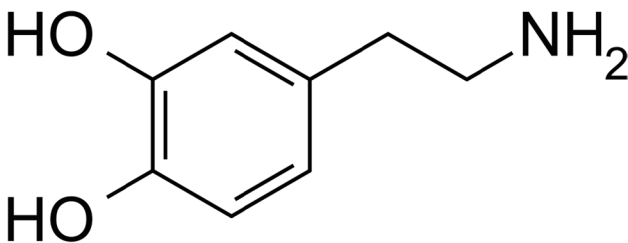


Fig. 2 Structure of dopamine

in the amygdala and nucleus accumbens (Gonzalez et al. 2007; Vyas 2015). These dopamine-containing regions play important functions, including basal ganglia in the control of movements, nucleus accumbens and hippocampus in learning, pleasure, memory, consciousness, dependence, information processing, and language (Prandovszky et al. 2011; Taupin 2007). In addition, the amygdala is associated with a range of cognitive functions, namely motivation, emotion, learning, cognition, memory, attention, perception, and fear (Baxter and Murray 2002; Prandovszky et al. 2011). Most of the effects of *T. gondii* infection are reported in the hippocampus and amygdala (Dalimi and Abdoli 2012). The

T. gondii genome includes two aromatic acid hydroxylase genes (i.e., AAH1 and AAH2) that encode tyrosine and phenylalanine hydroxylases (Gaskell et al. 2009). These enzymes catalyze phenylalanine to tyrosine and tyrosine to 3,4-dihydroxyphenylalanine (L-Dopa), as the direct precursor of dopamine, that could directly affect dopamine and/or serotonin biosynthesis. These enzymes result in the alteration of the host behavior (Elsheikha and Zhu 2016). In addition, it has been reported that TH identified within *T. gondii* cysts is encoded by the parasite itself (Prandovszky et al. 2011). The expression of the AAH2 gene increased in the dormant bradyzoite stage (Webster et al. 2006); however, the results of a study showed that the disruption of the AAH2 gene had no effect on the growth and differentiation of the parasite, as well as the global dopamine levels of the brain (Z. T. Wang et al. 2015). Another study reported that the AAH gene plays a role in the enhancement of the ability to transmit infection in cats (Z. T. Wang et al. 2017). This section addresses several mechanisms by which the parasite may alter dopamine levels.

Role of cytokines and enzymes

Macrophages and dendritic cells (DCs) secrete interleukin-12 (IL-12) during the stimulation of *T. gondii* antigen. Toll-like receptors (TLR)-11/TLR-12 dimer is important for DC response and IL-12 production (Koblansky et al. 2013; Andrade et al. 2013). In fact, mice lacking TLR-11 produce lower levels of IL-12 (Yarovinsky et al. 2005; Sher et al. 2017), and a lack of TLR-12 results in a loss of resistance to toxoplasmosis as well as a deficiency in the MyD88 encoding gene (Yarovinsky et al. 2005; Sher et al. 2017). Mice deficient in the MyD88 adapter molecule are highly sensitive to toxoplasmosis (Koblansky et al., 2013). The IL-12 maintains a long-lasting immune response in the chronic stage of infection. The IL-12 also activates the production of interferon-gamma (IFN- γ) by natural killer (NK) cells and T cells (Hunter et al. 1995; Yap et al. 2000). The IFN- γ is the most important cytokine regarding resistance to *T. gondii* that can eliminate the parasite and inhibit its proliferation through specific mechanisms (Dupont et al. 2012). One of these mechanisms is releasing indoleamine 2,3-dioxygenase (IDO) (F. Wang and Lidow 1997). This enzyme induces the degradation of tryptophan (Pfefferkorn 1984), and kynurenic acid (KA) and quinolinic acid (QA) are the products of tryptophan catabolism in the brain that increase oxidative stress, damaging cells, and apoptosis (Schwarcz et al. 2012). In human patients, high levels of QA and KA are associated with many neurological disorders, such as SZ and depression (Notarangelo et al. 2014; Schwarcz and Pellicciari 2002). In addition, in baseline conditions, kynurenine is mainly metabolized to KA, and the accumulation of this catabolite in the CNS due to its N-methyl-D-aspartate (NMDA) antagonistic properties can alter dopamine metabolism (Hilmas et al. 2001; Mortensen et al. 2007). Also, KA is an antagonist to alpha 7 nicotinic acid receptor and increases the release of amphetamine-stimulated dopamine in the striatum (Elsheikha and Zhu 2016). A seven-fold increase in KA has been reported in the brains of animals infected with *T. gondii* (Tedford and McConkey 2017). Medications known as dopamine-releasing agents, such as amphetamine, can exacerbate psychotic symptoms in patients and cause psychiatry in normal people (Laruelle et al. 1996). Chronic *T. gondii* infection can produce an abnormal response to dopamine stimulant, and behavioral deficits in response to amphetamine have been observed in mice infected with *T. gondii* (Xiao et al. 2016). Another enzyme that may affect dopamine levels is catechol-O-methyltransferase. This enzyme as a candidate gene for some psychiatric disorders, such as suicidal behaviors, is the major dopamine-degrading enzyme in the prefrontal cortex (Cáceda 2014). However, the expression of this gene was not significantly different in *Toxoplasma*-infected mice, compared to that reported for the

controls (Xiao et al. 2014). Monoamine oxidase A (MAOA) is an enzyme that plays an important role in the metabolism of biogenic amines such as dopamine; in rodents, the infection with *T. gondii* results in the decrease of this enzyme (Cáceda 2014; Xiao et al. 2014). The decreased activity of this enzyme is associated with personality features, such as impulsivity and aggression. In addition, the increased activity of this enzyme leads to a decrease in dopamine levels that is associated with mood disorders and aggressive behaviors (Cáceda 2014).

Another point is that IFN- γ causes tissue damage via mechanisms, such as the production of NO and the destruction of dopamine-producing neurons (Kusbeci et al., 2011). This cytokine and other pro-inflammatory cytokines (e.g., IFN- α and IFN- β) activate guanosine triphosphate cyclohydrolase 1 (GTP-CH1) that leads to the increased production of neopterin [increasing the concentration of NO via the creation of tetrahydrobiopterin (BH4)] and decreased levels of amino acids phenylalanine and tyrosine. The two above-mentioned amino acids are precursors for the biosynthesis of dopamine. The BH4 plays a role in the synthesis of dopamine (Neurauter et al. 2008). Cytokines can decrease dopamine accessibility in related brain areas by reducing the concentrations of BH4 (Kitagami et al. 2003). Moreover, cytokines and inflammatory mediators show that *Toxoplasma*-induced encephalitis may affect neurotransmitters through the activation of mitogen-activated protein kinases (MAPK) (Zhu et al. 2005; Zhu et al. 2010). The activation of MAPK pathway can have a dual effect on dopamine. Also, murine TLR-11 and 12 of DCs, recognize a *Toxoplasma* pathogen-associated molecular pattern (Profilin) to primarily signal through the adaptor protein MyD88, leading to the activation of MAPK (Koblansky et al., 2013; Yarovinsky et al. 2005; Sanecka and Frickel 2012; Arnold-Schrauf et al. 2015). Profilin is essential for the invasion and active egress of *T. gondii* from the cells (Egan et al. 2009; Kucera et al. 2010; Plattner et al. 2008). Imiquimod (an efficient immunomodulatory drug against certain viral and parasitic infections) upregulates the expression of TLRs 7, 11, and 12, following interconversion from bradyzoites to tachyzoites. As a result, the MyD88 pathway is activated, leading to the induction of an immune response to control *Toxoplasma* foci (Hamie et al., 2021).

The MAPK signaling results in reduced dopamine recycling and overstimulation of its receptors (Zhu et al. 2005, 2010). The decreased synthesis of dopamine is associated with the disruption of sleep, fatigue, as well as gastrointestinal and musculoskeletal disorders (Hsu et al. 2014). Another point about dopamine is the presence of a relationship between dopamine and sex hormones, such as testosterone, both of which increase during latent toxoplasmosis (Hull et al. 2004). Testosterone increases the synthesis of NO in the medial preoptic area (Hull et al. 2004). The mediator of

the connection between testosterone and dopamine is NO because NO and other inflammatory cytokines, such as IL-2 and IL-6, increase dopamine levels (Hull et al. 2004; Prast and Philippu 2001; West et al. 2002). Moreover, increasing testosterone enhances dopamine levels (Hull et al. 1995). Another mechanism by *T. gondii* for impaired dopamine signaling is the in vitro upregulation of microRNA-132 (Tyebji et al. 2019). MicroRNAs are a class of small noncoding ribonucleic acids involved in regulating gene expression (Lamadrid-Romero et al. 2018; Lim et al. 2005). Changes in host miRNAs following *T. gondii* infection are mainly related to immunity and apoptosis processes (Xu et al. 2013). The miR-132 regulates neuronal and immune functions and is involved in the differentiation of dopamine neurons (Yang et al. 2012; Wanet et al. 2012). Also, miR-132 upregulation modulates a set of important pathways that have a critical role in vital brain functions, translational initiation and regulation, meiosis, mitosis, carcinogenesis, and cell growth, differentiation, survival, and proliferation (Xiao et al. 2014). The dysregulation of microRNA-132 expression can be associated with various behavioral and neuropsychiatric disease models, such as SZ, AD, and PD, in humans and animals (Hinze-Selch 2015; Miller et al. 2012; Wanet et al. 2012). The microRNA-132 expression was down-regulated during chronic infection (Li et al. 2015; Remenyi et al. 2013; Yang et al. 2012); nevertheless, acute *T. gondii* infection had an opposite effect (Li et al. 2015). The parasite probably needs these changes at the stage chronic in its life cycle to have complete control over the host cell (Abo-Al-Ela 2019). In addition to these mechanisms, a substance may play a role in the development of mental disorders; one study investigated the effects of exposure to *T. gondii* alone and methylmercury (MeHg), along with *T. gondii* in vivo. The obtained results showed that MeHg and *T. gondii* had synergistic effects and significantly increased the number of cysts in the brains of mice (King et al. 2003). Thimerosal, an organic-mercury compound used as a preservative in vaccines and serum to block the growth of contaminants in biological materials (Fernandes Azevedo et al. 2012), inhibits dopamine-stimulated methylation reactions in the body. These reactions are important for growth factors and promotion of normal neuronal growth (Waly et al. 2004).

Serotonin

Serotonin is a neurotransmitter involved in the pathogenesis of some psychiatric disorders, such as depression, which vary with *T. gondii* infection (Fig. 3) (Mahmoud et al. 2016; Oxenkrug 2013; Tyebji et al. 2019). Moreover, serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter released from serotonergic neurons. The neurons that produce serotonin are located in the midbrain, hypothalamus, substantia

nigra, pineal gland, and raphe nuclei of the brain stem (Herlenius and Lagercrantz 2004). In humans, serotonergic neurons appear in 5–12 weeks of pregnancy (Herlenius and Lagercrantz 2004). Serotonergic cells send axons to the anterior part of the brain, and these cells could play an important role in the differentiation of neural precursors (Gaspar et al. 2003). Serotonin receptors are divided into 7 families (i.e., 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇) and 14 subtypes (i.e., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₃, 5-HT₄, 5-HT_{5A}, 5-HT_{5B}, 5-HT₆, and 5-HT₇). Most of the 5-HT receptors belong to the G-protein receptor family, and only 5-HT₃ receptors are ligand-gated ion channels (Abg Abd Wahab et al. 2019). Serotonin plays an important role in innate and acquired immune responses and affects the secretion of cytokines by stimulating lymphocytes and monocytes (Durk et al. 2005). This neurotransmitter acts as a significant mediator in inflammatory processes, as well as endocrine and autonomic system (Ohno 2011). Serotonin modulates the inflammation of the nervous tissue, cell division, neuronal migration, cell differentiation, synaptogenesis, and motor behavior (Abg Abd Wahab et al. 2019; Gaspar et al. 2003). It also plays an important role in the regulation of important physiological processes, such as motor activity, body temperature, pain, sleep, cognitive function, and emotional behaviors (Ohno 2011). The tachyzoite phase of *T. gondii* requires tryptophan to replication (Fabiani et al. 2013). Tryptophan is catabolized by two pathways, including one through the kynurenine pathway and the other through tryptophan 5-hydroxylase decarboxylation, to form serotonin (Hsu et al. 2014). The biosynthesis of serotonin may be directly affected by two genes, namely AAH1 and AAH2, in the genome of *T. gondii* (Fuglewicz et al. 2017). Furthermore, serotonin may be involved in innate fear behavior (e.g., rodent avoidance of cat odors), and *T. gondii*-stimulated IFN- γ can potentially affect the attraction and loss of fear for predator odor in

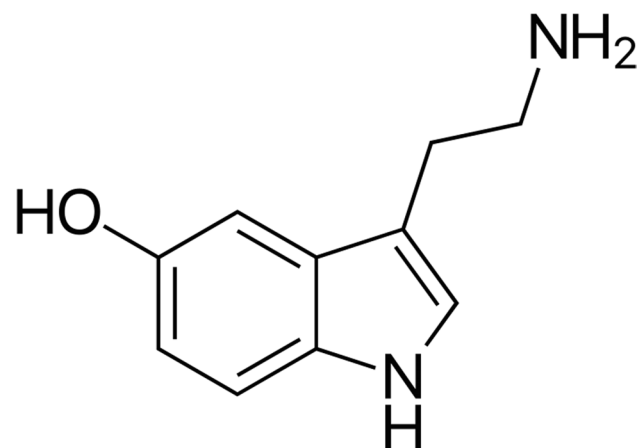


Fig. 3 Structure of serotonin

rodents (Graeff et al. 1997). These behavioral changes associated with chronic *T. gondii* infection may have an effect on neural and glial cysts, disruption of neurotransmitters, such as serotonin, and local inflammatory responses in the brain (Hurley and Taber 2012). The impaired metabolism of neurotransmitters, transporters, and their receptors has been associated with various types of pathological manifestations (e.g., the role of serotonin in depression) (Hamon and Blier 2013; Parlog et al. 2015). In addition, different neurotransmitters interact with each other in regulating the excitation and inhibition of motor neurons (Wagner et al. 2017). For example, serotonin plays a role in the reduction or enhancement of glutamate-mediated transmission and GABA-mediated transmission in motor structures (Ciranna 2006). Factors that alter serotonin levels are discussed in the following sections.

Role of indoleamine 2, 3-dioxygenase

The infection with *T. gondii* induces a strong type 1 T helper (Th1) immune response in which IFN- γ , IL-12, and killer T cells play a major role (Munoz et al. 2011). The IFN- γ and some cytokines, such as IL-2, induce the release of IDO, catabolizing tryptophan (Muller and Schwarz 2006; Tan et al. 2012). Tryptophan is an essential amino acid and a precursor to serotonin biosynthesis; therefore, when the concentration of IDO increases during *T. gondii* infection, it may decrease the synthesis of this neurotransmitter (Schwarcz et al. 2012). Tryptophan metabolism induces the kynurenine pathway in which the tryptophan is catabolized and its products are the two neuroactive metabolites, namely QA and KA (Schwarcz and Pellicciari 2002). Increased KA concentration is a characteristic of SZ (Sophie Erhardt et al. 2001a, b); however, QA upregulation has been implicated in the etiology of many mental disorders, including AD (Gulaj et al. 2010), Huntington's disease (AL-Hadad et al. 2019; Guidetti et al. 2006), depression (Steiner et al. 2011), and autism spectrum disorder (Zimmerman et al. 2005), as well as in suicide attempts (Erhardt et al. 2013). The activation of the kynurenine pathway was reported in the brain of *T. gondii*-infected mice (Murakami et al. 2012).

Role of monoamine oxidase A

Serotonin is one of the biogenic amines that MAOA, a mitochondrial membrane enzyme, plays an important role in its metabolism (Courtet et al. 2005). It was reported that the infection with *T. gondii* reduced the in vivo expression of the MAOA gene (Sugden et al. 2016). Increasing the activity of this enzyme reduces the levels of serotonin (Courtet et al. 2005). The functional polymorphism of the MAOA gene has

been connected with anxiety, depression, autism, alcoholism, aggression, suicidality, and impulsiveness (Caspi et al. 2002; Caspi et al. 2003; Lau et al. 2009; Lesch et al. 1996; Nilsson et al. 2006; Nilsson et al. 2008; Sjoberg et al. 2006).

Activation of mitogen-activated protein kinases

During toxoplasmic encephalitis, several cytokines and inflammatory mediators are produced exerting their effect on neurotransmitters through the activation of the MAPK pathway (Haroon et al. 2012). This pathway controls various cellular processes, such as growth, differentiation, and stress responses. The stimulation of this pathway can enhance the function of the serotonin transporter and reduce serotonin at the level of the synapse (Zhu et al. 2005, 2010).

Glutamate

Glutamate is a nonessential amino acid whose metabolism and signaling are altered by *T. gondii* infection (Fig. 4) (Lang et al. 2018; Patri 2019). Since the 1950s, the excitatory action of glutamate has been described in the mammalian brain and spinal cord (Curtis and Watkins 1960; Hayashi 1952). In the late 1970s, glutamate was identified as the main excitatory transmitter in the vertebrate nervous system (Meldrum 2000). This neurotransmitter is synthesized from glucose and other precursors and cannot cross the blood–brain barrier (Patri 2019). The overproduction of glutamate occurs in the early postnatal period (e.g., after 1–2 weeks in the rat cortex and following 1–2 years in the human cortex) (Benítez-Díaz et al. 2003; Herlenius and Lagercrantz 2004). Given that glutamate is involved in different metabolic pathways, it is critical for maintaining normal CNS function (Abg Abd Wahab et al. 2019; Bak et al. 2006). Five types of glutamate transporters are known, including excitatory amino acid transporter 1, excitatory amino acid transporter 2, excitatory amino acid transporter 3, excitatory amino acid transporter 4, and excitatory amino acid transporter 5 (Y. Zhang et al. 2016). Glutamate receptors are located on neuronal and nonneuronal cells and involved in the regulation of many cognitive processes (Daikhin and Yudkoff 2000; Dauvermann et al. 2017). Alterations in the function or expression of the glutamate transporters (i.e., excitatory amino acid transporters [EAATs]) are shown in the pathogenesis of many psychiatric disorders, such as AD and PD (Benarroch 2010). The EAATs are involved in the prevention of glutamate dysregulation by controlling its release and reuptake. These transports can also play a role in neuronal development, memory, excitotoxicity, learning, pain perception, and motor behavior regulation (Patri 2019; Zhang et al. 2016). In

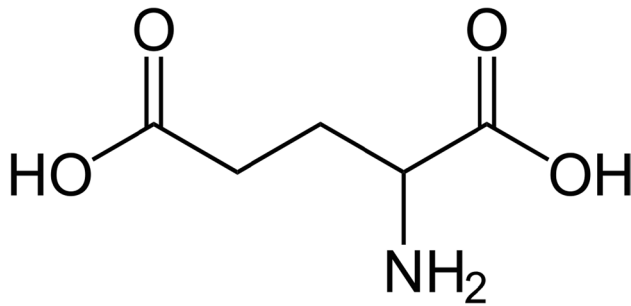


Fig. 4 Structure of glutamate

addition, glutamate interacts with other neurotransmitters. In this regard, serotonin plays a role in glutamate-mediated transmission in the control structures of movement (Ciranna 2006; Wagner et al. 2017). The chronic infection of *T. gondii* results in a two-fold reduction in the expression of the glutamate transporter 1 (GLT-1) in glial cells and increase extracellular glutamate (David et al. 2016).

Activation of N-methyl-D-aspartate receptor

The activity of IDO is mostly stimulated by IFN- γ , and the release of this enzyme results in the destruction of tryptophan (Dalimi and Abdoli 2012; Tedford and McConkey 2017). Tryptophan is an essential amino acid required for the growth of *T. gondii*; therefore, the growth of parasite is inhibited by decreasing the concentration of this amino acid (Cerávolo et al. 1999). Kynurenine is mainly metabolized to KA; however, the major product of kynurenine metabolism is QA in inflammatory conditions (Hilmas et al. 2001; Saito et al. 1992). The QA, an NMDA agonist produced by microglia, binds to glutamate N-methyl-D-aspartate receptors (NMDARs) (Guillemin et al. 2005; Schwarcz and Pellicciari 2002). The NMDAR plays an important role in the pathophysiology of several mental disorders, such as SZ (Javitt 2014; Moghaddam and Javitt 2012; Papouin et al. 2017), and it has been suggested as the mechanistic link between *T. gondii* infection and onset of SZ (Lucchese 2017; Tao Wang et al. 2013). Kannan *et al.* showed that exposure to *T. gondii* leads to the production of serum IgG antibodies to NMDARs. This change may provide the condition for a reduction in the function of glutamate receptors, and related disorders have been observed in SZ (Geetha Kannan et al. 2016; Kannan et al. 2017). Furthermore, the evaluation of *T. gondii* seronegative SZ patients and seropositive non-SZ controls showed lower NMDA IgG titers, compared to those reported for seropositive individuals with SZ (G Kannan et al. 2017). The activation of NMDAR stimulates excitotoxicity and oxidative stress in the brain (Elsheikha and Zhu 2016). On the other hand, KA, an antagonist of NMDAR produced in astrocytes, reduces glutamatergic neurotransmission and can

lead to cognitive deficits (Goff 2015; Guillemin et al. 2005; Kegel et al. 2014; Schwarcz and Pellicciari 2002). In addition, KA has been implicated in the inhibition of alpha 7 nicotinic acetylcholine ($\alpha 7nACh$) receptors and modulation of glutamatergic neurotransmission (Beggiato et al. 2013). Glutamate converts to glutamine by glutamine synthetase, and changes in glutamine increase calcium entry into neurons which may play a role in excitotoxicity and altered neurotransmission (Elsheikha and Zhu 2016; Shen 2013). Some of the mechanisms affecting glutamate levels are discussed in the following sections.

Interaction of glutamate and gamma-aminobutyric acid

The GABA is an inhibitory neurotransmitter that may play a key role during *T. gondii* infection. This neurotransmitter is able to regulate glutamate signaling. The glutamic acid decarboxylase 67 (GAD67) converts glutamate to GABA. In infected animals, general changes are observed in the localization of GAD67; nevertheless, the GABAergic pathway remains intact (Brooks et al. 2015). In mice infected with *T. gondii*, the number of tissue cysts was low; however, the location of GAD67 was impaired throughout the brain. Finally, impaired GABAergic signaling and/or increased glutamate can cause neurophysiological outcomes, such as seizures, associated with *T. gondii* infection (Treiman 2001).

Decreased expression of glutamate transporter 1

A significant reduction in GLT-1 and a significant increase in CNS extracellular levels of glutamate were observed during *T. gondii* infection (David et al. 2016). In pathological conditions and dysregulation of the glutamate transporter expression and/or function, excess extracellular glutamate causes the death of excitotoxic cells in surrounding postsynaptic neurons by the overactivation of ionotropic glutamate receptors (Choi 1994). Several studies have shown the anti-toxoplasmic effect of antipsychotic drugs on the inhibition of in vitro parasite proliferation; nonetheless, other studies have not demonstrated an in vivo effect. Ceftriaxone is a beta-lactam antibiotic that increases GLT-1 expression (Rothstein et al. 2005). Ceftriaxone reduced infection-induced extracellular glutamate concentrations and was neuroprotective in mice. However, it had no effect on the immune response to the infection and behavioral deficits in mice (David et al. 2016).

Gamma-aminobutyric acid

The GABA is another neurotransmitter that appears to play a role in the mechanisms of anxiety and depression in the mammalian CNS (Fig. 5) (Kalueff and Nutt 2007), and its levels vary with *T. gondii* infection (Lang et al. 2018). The GABA, the most ubiquitous inhibitory neurotransmitter in the CNS, was identified in 1883. The main role of GABA is to modulate the flow and timing of excitatory neurotransmitters, such as glutamate, thereby preventing seizures (Bazemore and Florey 1956; Treiman 2001). Its inhibitory role was firstly introduced in the late 1950s by Bazemore and Florey (Bazemore and Florey 1956). The GABA is considered an important transmitter for the human infant, and the elimination of vitamin B₆ from the human infant formula can lead to deadly consequences. The GABA deficiency is the major cause of these consequences and results in fatal seizures (Frimpter et al. 1969). The infection with *T. gondii* causes GABA release from the DCs (Fuks et al. 2012), and this protozoan uses this neurotransmitter as a carbon source (MacRae et al. 2012). The GABA is not a product of intermediary metabolism and is not used in protein synthesis. Moreover, it is produced in the neuronal tissue of glutamate by alpha decarboxylation of glutamic acid in the presence of GAD (Patri 2019). Probably 25–40% of nerve terminals contain GABA (Marín and Rubenstein 2001). About 95% of GABAergic cells are located in the striatum. The GABA activity can also be observed elsewhere, such as the cerebral cortex, lateral vestibular nucleus, and spinal cord (Patri 2019). There are two types of rapid and slow inhibitory receptors (i.e., ionotropic GABA_A and metabotropic GABA_B, respectively) (Herlenius and Lagercrantz 2004; Patri 2019). Ionotropic receptors increase Cl⁻ ion conductance; however, metabotropic receptors indirectly change membrane ion permeability and neuronal excitability (Stein and Nicoll 2003). Given that different neurotransmitters interact, any disturbance in glutamate levels and signaling during *T. gondii* infection can exacerbate changes in GABA signaling in the brain (Ngô et al. 2017; Ngoungou et al. 2015; Palmer 2007; Tyebji et al. 2019). The neurophysiological outcomes are the result of the disruption of GABAergic signaling and elevated glutamate levels

(Treiman 2001). The GABA activates GABA_A receptors on *Toxoplasma*-infected DCs leading to a hypermigratory phenotype in those cells. This process was assumed to be a tool for parasite propagation (Brooks et al. 2015). Moreover, in order to regulate motor neurons, various neurotransmitters, such as serotonin and GABA, interact (Wagner et al. 2017). For example, GABA-mediated translocation occurs in structures controlling the movement affected by serotonin (Ciranna 2006). The following factors alter GABA levels.

Role of interferon-gamma

The IFN- γ production is the first line of defense against *T. gondii* infection. The IFN- γ is produced by NK and T cells (Hunter et al. 1996). The chemokines, such as chemokine (C–C motif) ligand 5 (CCL5), chemokine (C–X–C motif) ligand 9 (CXCL9), and chemokine (C–X–C motif) ligand 10 (CXCL10), are expressed by astrocytes and microglia during *T. gondii* infection in the brain. These compounds attract the produced IFN- γ to *T. gondii* antigens and lead to parasite release (Yasuhiro Suzuki et al. 2011). Macrophages are among the IFN- γ -activated cells that express C–C chemokine receptor type 5 in these cells. Activated macrophage prevents the proliferation of *T. gondii* tachyzoites (Denkers and Gazzinelli 1998). The combined expression of the three chemokines (i.e., CCL5, CXCL9, and CXCL10) plays an important role in maintaining the Th1 response and facilitating macrophage migration to the brain in order to control the parasite (Imtiaz A Khan et al. 2000). The IFN- γ plays an important role in the regulation of the behaviors, such as anxiety, depression, as well as cognitive memory, and *T. gondii* infection can disrupt these behaviors (Gonzalez et al. 2007; Mahmoud et al. 2017; Mahmoud et al. 2016). Moreover, IFN- γ increases tonic GABAergic inhibitory current and latency of seizure onset and reduces the severity of the seizure. A study reported that IFN- γ is involved in the regulation of GABAergic signaling and social behaviors in mice. Social deficits in IFN- γ knockout mice are rescued by the use of diazepam, a GABA activator (Tyebji et al. 2019). Diazepam increases the affinity of GABA to the GABA_A receptor (Lavoie and Twyman 1996). The infection with *T. gondii* tissue cysts leads to changes in the distribution of GABA in the brain, which could disrupt the social activities that IFN- γ regulates in infected mice (Brooks et al. 2015; Tyebji et al. 2019). In IFN- γ knockout mice, disorders, such as depression and anxiety, increase and neurogenesis decreases in the hippocampus (Campos et al. 2014). Under the basal condition, IFN- γ knockout mice displayed impaired spatial recognition memory; however, in chronic stressful conditions, such as *T. gondii* infection, IFN- γ knockout mice exhibited enhanced memory function. This finding suggests

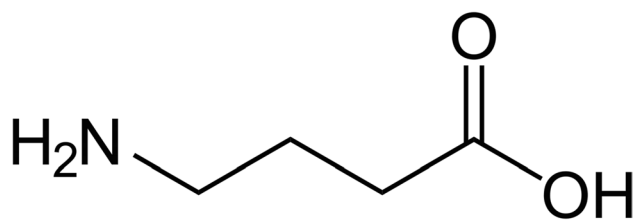


Fig. 5 Structure of GABA

that IFN- γ signaling during infection may worsen memory impairment (Litteljohn et al. 2014; Tyebji et al. 2019).

Dysregulation of glutamic acid decarboxylase 67

The major part of GABA (90%) in the CNS is produced by GAD67 as a structurally active enzyme; nevertheless, GAD65 is temporarily activated. The GAD65 plays a role in the rapid modulation of inhibitory neurotransmission (Asada et al. 1997; Condie et al. 1997). The GAD67 is the main enzyme for the neuronal biosynthesis of GABA and converts glutamate to GABA. The GABA is involved in the regulation of glutamate signaling (Brooks et al. 2015). The effect of *T. gondii* infection on GAD65 levels has not been studied (Tyebji et al. 2019); nevertheless, the infection with *T. gondii* causes spontaneous seizures and in vivo redistribution of GAD67 (Brooks et al. 2015). The cause of the seizures in mice with toxoplasmic encephalitis is certain changes in synaptic localization of GAD67 and impairment of GABAergic cells that can lead to extracellular accumulation of glutamate. One of the symptoms of MDD is GABAergic dysfunction in the prefrontal cortex (Croarkin et al. 2011; Karolewicz et al. 2010; Levinson et al. 2010; Tedford and McConkey 2017). This phenotype was also observed in the animal models of *T. gondii* infection (Mahmoud et al. 2017, 2016). *T. gondii* is directly involved in inhibitory neurotransmission and provides a molecular basis for the occurrence of various neurological consequences in patients with toxoplasmic encephalitis (Brooks et al. 2015).

Norepinephrine (Noradrenaline)

Norepinephrine is another neurotransmitter the infection of which with *T. gondii* affects its levels (Fig. 6) (E Fuller Torrey and Yolken 2003). Alteration in the levels of this neurotransmitter has been observed in various mental disorders, such as SZ, completed suicide, and suicide attempts (Arango et al. 1996; Ordway et al. 1994; E Fuller Torrey and Yolken 2003). The appearance of noradrenergic neurons occurs in the early stages of pregnancy (i.e., 12–14 days in mice and 5–6 weeks in humans) (Sundström et al. 1993). Norepinephrine is primarily produced in the brainstem neurons of the locus coeruleus and subcoeruleus, as well as several other nuclei (Xu et al. 2000). The effects of noradrenaline are mediated by adrenergic receptors. These receptors are divided into three main types (i.e., alpha-1, alpha-2, and beta), and each type of receptors is classified into three subtypes. These receptors are widely expressed throughout the CNS and in almost all peripheral tissues (Ahlquist 1948; Bylund et al. 1994). Among the adrenergic sites, alpha-2

adrenergic receptors are abundant, and these receptors spread throughout all the regions of the transient embryonic cortical (F. Wang and Lidow 1997). Norepinephrine is involved in regulating a number of physiological processes, including mood, sleep, arousal, aggression, memory, alertness, blood flow, and metabolism, as well as the endocrine and autonomic nervous systems (Axelrod and Kopin 1969; Feldman et al. 1997; Wang et al. 1999). The reduction in the concentration of this neurotransmitter has been reported in a variety of motor disorders in humans that may explain the possible relationship between toxoplasmosis and motor disorders (Nath et al. 1993; Rommelfanger et al. 2007). Ihara et al. in 2016 reported a reduction in norepinephrine levels in the cortex and amygdala in mice infected with *T. gondii* (Ihara et al. 2016). The results of another study showed that norepinephrine levels in mice infected with acute infection decreased by 28% (Stibbs 1985). In addition, latent toxoplasmosis can reduce the aversion of rodents to cat odors (Berdoy et al. 2000). These behavioral changes associated with latent *T. gondii* infection may impair the norepinephrine neurotransmitter (Hurley and Taber 2012), and the cortical noradrenergic system may play a role in fear avoidance (Andrews et al. 1993). The data on the changes in the levels of neurotransmitters in rats with high avoidance of cat odor demonstrated an increased cortical noradrenaline level after the exposure to cat odor (Andrews et al. 1993). There are several mechanisms involved in rodent aversion to cats. For example, the cat odor activates the wolfram gene in the amygdaloid region. Activation of this gene occurs in parallel with the activation of carboxypeptidase E, suggesting a possible role for wolframine in neuropeptide synthesis (Köks et al. 2002). Mutations of the wolfram syndrome 1 (WFS1) gene are responsible for wolfram syndrome that is characterized by further neurological and endocrinological abnormalities. The WFS1 gene encodes wolfram. The function of the wolfram protein, a multispreading membrane glycoprotein of the endoplasmic reticulum, is not yet fully perceived

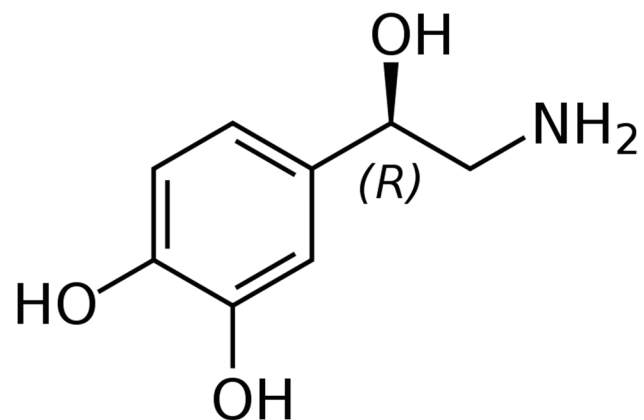


Fig. 6 Structure of norepinephrine

(Hofmann et al. 2003). Despite the fact that its function is unknown, there is some evidence that wolframin mutations may predispose people to affective disorders. Swift *et al.* reported that 60% of wolfram syndrome patients showed psychiatric symptoms (Swift et al. 1998). Moreover, there is a node of the extra-hypothalamic vasopressinergic system in the poster-dorsal medial amygdala (MePD) of rats that contains many arginine vasopressin (AVP) neurons. *T. gondii* causes hypomethylation of the AVP promoter, resulting in increased expression of this peptide in the MePD of infected male rats. Infected animals exposed to cat odor show activation of vasopressinergic neurons and the accompanying loss can be reversed by the systemic hypermethylation of the MePD-AVP (Hari and Vyas 2014). These behavioral changes may be due to altered neurochemical pathways, including norepinephrine, as well as the presence of cysts in the brain (Klein 2003). There have been also several studies with contradictory results. For example, a systematic review examining the role of hormones in *T. gondii* infection reported a lack of association between noradrenaline and *T. gondii* (Galvan-Ramirez Mde et al. 2014). The following sections discuss several mechanisms involved in norepinephrine levels.

Activation of guanosine triphosphate cyclohydrolase 1

The stimulation of IFN- γ and other proinflammatory cytokines results in GTP-CH1 activity. The activity of this enzyme leads to a decrease in phenylalanine and tyrosine. Since phenylalanine is a precursor of norepinephrine, lowering its levels results in the reduced synthesis of this neurotransmitter (Capuron et al. 2011; Sperner-Unterweger et al. 2014). In addition, since several cells metabolize dopamine to norepinephrine, the reduction of phenylalanine and tyrosine amino acids as the precursors of dopamine also affects the levels of norepinephrine produced (Capuron et al. 2011; Prandovszky et al. 2011).

Decreased expression of monoamine oxidase A

The MAOA and monoamine oxidase B (MAOB) play an important role in the metabolism of neurotransmitters and dietary amines (Grimsby et al. 1991). The MAOA preferentially oxidizes biogenic amines, such as norepinephrine, and is inactivated by acetylenic inhibitor clorgyline (Grimsby et al. 1991). The reduction of MAOA expression was demonstrated in mice with *T. gondii* infection. Five days after the infection, a 55% reduction in the expression of this enzyme was reported in the striatum of mice brain, compared to that

reported for the controls (Xiao et al. 2014). The abnormal levels of monoamine oxidase (MAO) activity have been reported in some psychotic disorders, such as SZ (Wyatt and Murphy 1976), depression (White et al. 1980), and alcoholism (Sullivan et al. 1979). In addition, MAO inhibitors have been used as antidepressants (Murphy et al. 1984).

Epinephrine (Adrenaline)

Epinephrine is another neurotransmitter whose levels may be affected by *T. gondii* infection (Fig. 7). It has been shown that depression and suicidal behaviors are often associated with an imbalanced immune response and metabolism of neurotransmitters, such as epinephrine (Capuron and Miller 2011; Haroon et al. 2012; Sperner-Unterweger et al. 2014). Epinephrine was the first hormone to be isolated into the pure state in 1900 by Jokichi Takamine (Scanzano and Cosentino 2015). Three α_1 (i.e., α_{1a} , α_{1b} , and α_{1d}), three α_2 (α_{2A} , α_{2B} , and α_{2C}), and three β (i.e., β_1 , β_2 , and β_3) are major types of adrenergic receptors. Furthermore, these receptors are among the best described G protein-coupled receptors (Cotecchia et al. 2012). Multiple studies have reported a relationship between these behavioral changes and alterations in the concentration of neurotransmitters (Jaroslav Flegr and Kuba 2016; Skalova et al. 2006). According to the evidence, it was shown that urinary epinephrine excretion during a cognitive challenge in ADHD subjects was at least 40% lower than that reported for the control group (Pliszka et al. 1994). Another study investigated the effect of congenital *T. gondii* infection on the behavior and concentration of neurotransmitters. Only the impact of congenitally *T. gondii* infection on the short-term memory behavior of male rats showed a significant difference, compared to that reported for the control group. The results of the aforementioned study did not confirm the changes in neurotransmitters caused by chronic *T. gondii* infection (Goodwin et al. 2012).

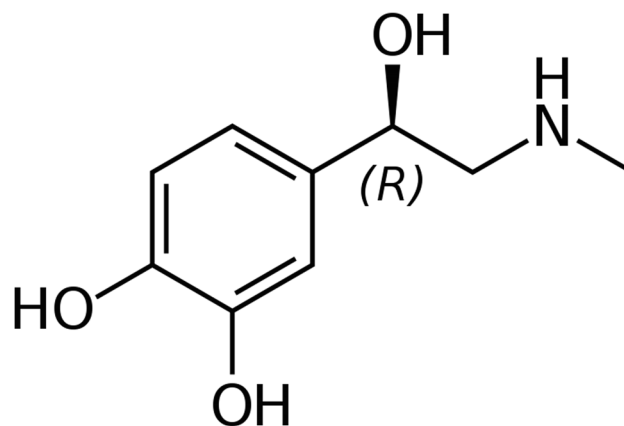


Fig. 7 Structure of epinephrine

Another study examined the effects of chronic toxoplasmosis on the levels of some neurotransmitters, such as dopamine, adrenaline, and noradrenaline, in human serum. The findings of the aforementioned study showed that the serum levels of adrenaline were significantly higher in patients with latent toxoplasmosis, compared to those reported for the control group (AL-Hadad et al. 2019). In addition, a systematic review by Galván-Ramírez in 2014 investigated the role of hormones in *T. gondii* infection. Based on the results, there was no association between adrenaline and *T. gondii* (Galvan-Ramirez Mde et al. 2014). MAOA with the following mechanism is effective in altering epinephrine levels.

Function of monoamine oxidase A

Epinephrine is one of the neurotransmitters catalyzed by the MAOA and MAOB (Grimsby et al. 1991). The changes in epinephrine levels have been observed in several mental disorders, such as AD (Tipton et al. 1984). The MAOA and MAOB are present in almost all human tissues except for the placenta that expresses most of the MAOA (Egashira 1976; Grimsby et al. 1990; Hsu et al. 1988), as well as platelets and lymphocytes that mainly show MAOB. In the fetal brain, MAOA is expressed before MAOB (Grimsby et al. 1990; Lewinsohn et al. 1980). Since *T. gondii* infection reduces the expression of the MAOA (87), it will probably affect epinephrine levels.

Acetylcholine

Acetylcholine is one of the most important neurotransmitters in the brain (Fig. 8) (Herlenius and Lagercrantz 2004). Multiple studies have indicated that the infection with *T. gondii* can interfere with several neurotransmitter systems, such as acetylcholine, leading to classical psychiatric illness (Anisman et al. 2008; Dunn and Wang 1995; Miller et al. 2009a, b). This neurotransmitter is important for the processes, such as cortical activation, pain, as well as memory, and counterbalances the effect of dopamine (Cooper et al. 2003; Johnston and Silverstein 2003). The cholinergic neurons in the brain are organized in subcortical regions, and the axons of these neurons spread in many areas of the brain, such as the cortex and hippocampus (Houser et al. 1985). These nerves play an important role in cortical growth, flexibility, and function (Hohmann 2003). The time of cholinergic nerve formation in the human fetus is about the 20th week and later than that reported for monoaminergic (Berger-Sweeney and Hohmann 1997). Cholinergic receptors are divided into nicotinic and muscarinic receptors and stimulated by nicotine or muscarinic drugs (Tiware et al. 2013). Nicotinic acetylcholine receptors may be associated with development

and flexibility. Moreover, the activation of these receptors creates synaptic contacts and wiring in the postnatal development period (Maggi et al. 2003). Chronic *T. gondii* infection affects cholinesterase activity and increases the level of acetylcholinesterase in the brain of infected mice. Acetylcholinesterase is a membrane-bound enzyme that hydrolyzes acetylcholine (Tonin et al. 2014; Alexandre Alberto Tonin et al. 2013). Therefore, various methods are used to improve the learning and memory impairments caused by *T. gondii* infection and reduce acetylcholine levels, including increasing the level of acetylcholine through synthesis promoters or using cholinesterase activity inhibitors (Giacobini 1996). One of these cholinesterase inhibitors is donepezil hydrochloride, which is used for the treatment of AD (Mahmoudvand et al. 2016). According to an animal study, it was observed that the treatment with this drug, in addition to improving memory, reduced β -amyloid in the brain of mice (Easton et al. 2013). Increased production of KA with the following mechanism affects acetylcholine levels.

Increased production of kynurenic acid

The infection with *T. gondii* in the CNS causes the strong activation of glial cells, especially astrocytes, which increase the production of KA in the brain (Müller and Schwarz 2007). The conversion of tryptophan to KA is due to tryptophan dioxygenase and IDO activity in the brain (Dalimi and Abdoli 2012). The KA is an endogenous antagonist of the $\alpha 7nACh$ receptor. This receptor is widely implicated in memory, learning, and cognitive processes (Schwarcz and Hunter 2007; Wonodi and Schwarcz 2010). The alteration of the concentration of endogenous KA in the brain can inhibit the $\alpha 7nACh$ receptors for acetylcholine (Müller and Schwarz 2007). The high levels of KA may lead to cognitive impairments (Schwarcz and Hunter 2007; Wonodi and Schwarcz 2010); for example, the high levels of KA were observed in the cerebrospinal fluid of schizophrenic patients (Erhardt et al. 2001a, b; Nilsson et al. 2005; Schwarcz et al. 2001).

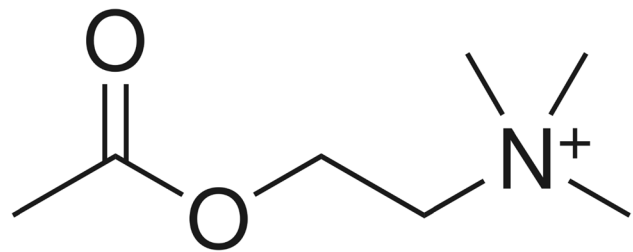
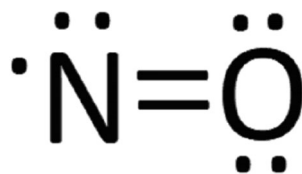


Fig. 8 Structure of acetylcholine

Nitric oxide (NO)

The NO has been identified as the first gasotransmitter. Gasotransmitters are vasoactive gaseous messenger molecules involved in different signaling processes (Fig. 9) (Mustafa et al. 2009). The NO is described as an endothelium-derived relaxing factor and produced in different types of mammalian cells. The production of NO by the NO synthase enzyme is carried out using L-arginine (Erdmann et al. 2013). This enzyme has three isoforms, including endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS), and inducible nitric oxide synthase (iNOS). The aforementioned isoforms are expressed in vascular endothelium and choroid plexus, neuronal cell bodies, as well as macrophages and glial cells, respectively. These three isoforms are produced in response to in vivo *T. gondii* infection (Dincel and Atmaca 2015; Tonin et al. 2014). An increase in intracellular Ca^{2+} leads to the activation of eNOS or nNOS, which results in NO production; however, iNOS-mediated NO production is independent of Ca^{2+} (Steinert et al. 2010). In physiological conditions, iNOS levels in the brain and arteries are low (Ortiz and Garvin 2003); nevertheless, in inflammatory conditions, such as *T. gondii* infection, iNOS levels are upregulated (Fujigaki et al. 2003). The NO, as a neurotransmitter in the brain, is involved in the processes of regulating memory and learning (Paul and Ekamparam 2011; Steinert et al. 2010), as well as in brain homeostasis, by cerebral blood flow during rest and under physiological conditions (Garry et al. 2015). *T. gondii* infection increases the production of NO (Butcher et al. 2001; Suzuki 2002) which is involved in killing and eliminating the parasite (I. A. Khan et al. 1997). Although NO production inhibits intracellular parasite replication, it has harmful and sometimes fatal effects on cells and infected mice (Sa et al. 2018). The NO production due to inflammation and resulting oxidative stress has been implicated in the etiology of psychiatric disorders, such as AD, PD, HD, as well as autoimmune diseases, such as multiple sclerosis (Bennett et al. 2009; Steinert et al. 2010). The NO and inflammatory cytokines, such as IL-2 and IL-6, are innate defenses against *T. gondii* infection (C. M. Miller et al. 2009a, b; Yarovinsky 2014) which in addition to their role in the etiology of psychiatric disorders contributes to the increasing levels of dopamine in the brain (Alonso et al. 1993; Petitto et al. 1997; Prast and Philippu 2001; West et al. 2002; Zalcman et al. 1994). IFN- γ alters the NO level with the following mechanisms.

Fig. 9 Structure of nitric oxide



Role of interferon-gamma

Neuroinflammatory responses are observed in chronic *T. gondii* infection. These responses are not confined to the areas surrounding the cyst and exert their effects throughout the CNS. *T. gondii* infection induces Th1 immune response (Dupont et al. 2012) and leads to the release of several cytokines, such as IFN- γ , IL-12, IL-1, IL-6, and TNF (Biswas et al. 2015, 2017; Carruthers and Suzuki 2007; Mohle et al. 2014; Wohlfert et al. 2017). The IFN- γ stimulates transforming growth factor beta-1 which, in turn, prevents the production of NO (Rozenfeld et al. 2005). As a result, the neuronal degeneration in the infected brain with *T. gondii* is limited (Mohle et al. 2016; Parlog et al. 2014). Therefore, this protective NO mechanism is used for the development of a vaccine against parasite in order to reduce parasitism in the brain (Czarnewski et al. 2017). The brain cyst burden is high in iNOS knockout mice (Sa et al. 2018); however, brain inflammation is lower than their parental lines, and there is no change in the levels of IFN- γ or TNF- α (I. A. Khan et al. 1997). Furthermore, the protective role of NO against *T. gondii* infection is tissue-specific (Scharton-Kersten et al. 1997). Despite the increase in *T. gondii* replication in the brain of iNOS knockout mice, the survival time of these mice increased after the infection (I. A. Khan et al. 1997). In addition, IFN- γ knockout mice had higher iNOS levels in the lungs but with lower levels of this enzyme in the brain than those reported for wild-type mice (Fujigaki et al. 2002). The IFN- γ knockout mice are not able to inhibit the growth of parasites (Jun et al. 1993).

Conclusion and future perspectives

The pathology of mental illnesses is a result of brain dysfunction. Since the brain is the most important site for the formation of *T. gondii* cysts, there might be various changes during the infection resulting in various mental illnesses of the brain. There is a hypothesis about the role of *T. gondii* infection in the pathophysiology of mental illnesses is to make changes in different neurotransmitters. There has been limited information on chronic *T. gondii* infection of the brain and its effects on behavior associated with changes in neurotransmitters. It is recommended to perform further studies in this field focusing on the observed alterations in neurotransmitters and impact of these changes on mental disorders. Furthermore, further studies are required to identify the effects of *T. gondii* infection on neurotransmitters and interactions of the immune system and neurotransmitters. Moreover, the alteration in the levels or functions of neurotransmitters can be due to changes in neurotransmitter receptors and receptor sensitivity that may be investigated

in future studies. There has been a high prevalence of latent toxoplasmosis in different countries, increasing prevalence of psychiatric disorders, increased probability of traffic accidents and working accidents, suicides, as well as other side effects of the infection associated with neurotransmitter changes. Therefore, it is required to perform further studies in countries with a higher prevalence of toxoplasmosis to elucidate the role of toxoplasmosis in neurotransmitters changes (especially less studied neurotransmitters, such as glycine, aspartate, and histamine) in psychiatric disorders. The perception of the link between *T. gondii* and neuropsychiatric diseases is important because it may provide an incentive to develop drugs and vaccines for the treatment or prevention from this infection, thereby eliminating one of the environmental factors that can cause problems in brain function. Future studies provide new perspectives on the prevention and treatment of these neurodegenerative disorders if they confirm the impact of *T. gondii* infection on neurotransmitters changes and their association with psychiatric disorders.

Authors' contributions

AD and TN review and wrote the manuscript; SS performed the literature research; AD supervised the review. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Data availability statement

No data was used for the research described in the article.

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Declarations

Ethical approval The code of ethics of this plan is (IR. MAZUMS. REC.1399.386).

Conflict of interest The authors declare that they have no conflict of interest.

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