Chapter 1

Dopamine, Neurotransmitters and Neuroparasites

HayriyeOrallar[1], Şeyda Karabörk[2], Çağrı Çamsarı[3], Kerem Yaman[4], Şule Aydın Türkoğlu[5] and Erol Ayaz[4]*

[1]Department of Poultry Sciences, Faculty of Agriculture and Natural Sciences, Abant Izzet Baysal University, Turkey
[2]Department of Medical Microbiology, Medical Faculty, Abant Izzet Baysal University, Turkey
[3]Innovative Food Technologies Center, Abant Izzet Baysal University, Turkey
[4]Department of Medical Parasitology, Medical Faculty Abant Izzet Baysal University, Turkey
[5]Department of Neurology, Medical Faculty, Abant Izzet Baysal University, Turkey

***Corresponding Author:** Erol AYAZ, Department of Medical Parasitology, Medical Faculty Abant İzzet Baysal University, Bolu, Turkey, MP: 05424599868; Tel: +90 374 254 10 00-1103; Fax:+90 374 253 45 0; Email: erolayaz68@hotmail.com

First Published **October 16, 2017**

Abstract

Dopamine is responsible for the control of many physical and mental mechanisms such as behavior, voluntary movements, motivation, stopping the production of prolactin, sleep, emotional state, attention, and learning. The disease occurs when it becomes diminished or increased because it controls too many mechanisms. For example, diseases such as schizophrenia occur when it is excessive and Parkinson's disease occurs when it is scarce. Recent studies have shown that dopamine modulates the immune system. After an infection in the brain, the amount of chemokines and cytokines increases, affecting the mechanism of Tryptophan, which reduces the formation of serotonin from tryptophan. On the other hand, in parasitic infections, particularly in the *T. gondii* infection, dopamine synthesis from tyrosine is increased in nerve cells infected with *T. gondii.* As a result, there are many parasites that settle in the brain. When these parasites enter the nerve cell, they first cytokines are secreted from

the astrocytes. They activate some enzymatic reactions on the host and increase the release of dopamine from Tyrosine while reducing serotonin and melatonin release from tryptophan. After the infection occurs, they first affect the amount of neurotransmitters by affecting each other through chain reactions after activation of the immune system. Behavioral changes and neuropsychiatric diseases arise afterward. With the understanding of these mechanisms, it will be possible to understand the causes of diseases such as schizophrenia, mood disorders, Parkinson's disease, Alzheimer's disease and epilepsy, which are very common in the world, and to develop new treatment methods.

Introduction

Dopamine

DA (C8H11NO2) was first synthesized in 1910 and experiments on its biological effects were started in the same year[1]. Thirty years after these studies, Peter Holtz and his colleagues found the L-DOPA decarboxylase enzyme in mammals and used this enzyme to obtain dopamine[2]. It has been determined in the 1950s that dopamine has an important physiological role in the mammalian brain, with the discovery of the presence of dopamine in peripheral tissues – even if in small amounts – and the identification of some of the biological processes [3].

The Physiological Role of Dopamine

Even though the dopaminergic neurons form only 1% of the neurons in the brain, they have tasks in quite different areas. Dopaminergic neurons are responsible for controlling many physical and mental mechanisms such as behavior and cognition, voluntary movements, motivation, stopping the production of prolactin, sleep, emotional state, attention and learning[4]. Dopaminergic neurons form a neural network deriving from ventral tegmental area (VTA), substantia nigra (SN) and hypothalamus [4].

Dopamine may exhibit toxic effects in the cell due to its high reactivity when its metabolism and storage do not occur under appropriate conditions [5]. Dopamine function follows the Yerkes-Dodson rule. Accordingly, the excessive or scarce level of dopamine may cause pathological reasons [6,7]. Disorders in dopaminergic neurons can lead to many disorders including schizophrenia, other psychiatric disorders and Parkinson's disease [5,8,9].

The Synthesis and Metabolism of Dopamine

The onset of dopamine production takes place with tyrosine, a non-essential amino acid taken with protein-rich foods. In dopaminergic neurons, the hydroxylation of tyrosine to L-DOPA is catalyzed by tyrosine hydroxylase (TH) enzyme. Tyrosine hydroxylase enzyme serves as a rate-controlling step in dopamine production[5].

Under normal physiological conditions, dopamine is placed in synaptic vesicles in the cytoplasm after being

synthesized via TH and aromatic amino acid decarboxylase (AADC) through vesicular monoamine transporter 2 (VMAT2) which is a 12-transmembrane domain protein from the soluble carrier protein family [5, 10]. Dopamine passes through the vesicular sinus via the vacuolar ATPase enzyme. This enzyme transports the protons (H^+) contained in the cytoplasm into the vesicles, thus creating the electrochemical gradient required by the vesicular membrane. This electrochemical gradient provides an exchange of a dopamine molecule versus two protons by allowing VMAT2 to act as antiporter [10]. Thus, VMAT2 is involved in the inhibition of accumulation of dopamine in the cytoplasm as resulting from its production or its transfer into synaptic vesicles [5].Dopamine is stabilized here under conditions of low pH, separated from synaptic vesicles and taken into dopamine carriers (DAT) [5]. After dopamine is taken into the synaptic opening, taking it back into the presynaptic neurons is accomplished via the dopamine transporters (DAT) [11].

When the amount of dopamine in the cytoplasm rises above the physiological values, Dopamine is metabolized via monoamine oxidase (MAO) and aldehyde dehydrogenase (ALDH) to 3,4-dihydroxyphenylacetic acid (DOPAC), a non-toxic metabolite. In addition, in astrocytes, catechol-*O*-methyltransferase (COMT) is catabolized to homovanillic acid (HVA) through MAO and ALDH[5].

Serotonin

Initial findings of serotonin as a neurotransmitter were obtained at the beginning of the 1950s[12]. Brain serotonin receptors were initially divided into two classes, serotonin receptor-1 (5-HT1) and 5-HT2 receptors. Up to now, nearly 15 serotonin receptors, some with effects opposite to each other, have been identified; it has been shown that there are seven different serotonin receptor families in the brain (5-HT1-7)[13]. In the human body, serotonin is produced and stored in nerve cells[14], in platelets [15], in gastrointestinal enterochromaffin cells and in prostatic neuroendocrine cells [16]. In addition, serotonin has an essential role in regulating growth differentiation and gene expression [17-19].

Serotonin and Dopamine Relation

Serotonin has several effects, especially behavioral, in many areas of the brain such as the amygdala hippocampus. With the help of these effects, it exhibits a regulatory effect on dopamine neurons. This effect theoretically also leads to a reduction in the risk of extrapyramidal side effects[20].

Serotonin has a repressive effect on mesocortical dopamine neurons. The effect of serotonin on dopamine is mediated by 5-HT2 receptors. With the blocking of 5-HT2, there is an increase in dopamine functions in the frontal lobe. An increase in dopamine in the frontal lobes

through the blocking of 5-HT2 or through another way leads to a decrease in negative symptoms[21]. In addition, 5-HT2 blockade exhibits an effect enhancing dopamine release in basal ganglia and in the nigrostriatal system. 5-HT2 receptors are found in presynaptic dopamine neurons. Induction of these receptors by serotonin causes a tonic inhibitory effect to emerge and the decrease of dopamine release[22].

Melatonin

The hormone which is synthesized from mammalian pineal gland in normal physiological conditions, melatonin (N-acetyl-5-methoxytryptamine) (MEL) is expressed only in the dark phase of the day, and it organizes the organism in the light-dark cycle [23-25]. Melatonin has an effect as a cellular preservative [23]antioxidant[26,27]and immunomodulator [24] in bacterial, viral and parasitic infections.It is responsible for the fundamental homeostasis such as the seasonal timing, sexual development, antioxidant protection system and immune response [28,29].

Melatonin is synthesized from tryptophan and is mainly released from the pineal gland, as well as the retina, lens, bone marrow, small intestine, and skin [30]. Today, there are 3 melatonin receptors in mammals. The M1 and M2 receptors are linked by G-proteins. The M3 receptor belongs to the family of quinone reductase. It was

isolated and chemically characterized in 1959[31]. It has a significant effect on many physiological and behavioral characteristics. Its one of the most important features is the regulation of circadian rhythm[32].

During inflammation against fungal and bacterial infections, the synthesis of melatonin from the pineal gland deteriorates and leukocyte migrates to the region where there is damage[33]. From macrophages[34,35]lymphocytes[36], melatonin is secreted for use in this process [37,38]. Melatonin also controls parasitic infections with its antioxidant properties. Melatonin treatment has been found to increase oxidative damage and survival of the *Schistosomamansoni*-infected mice[39]. It has been shown to reduce serious conditions affecting health in *Trypanosomacruzi* burden infections [40].

Acetylcholine

Acetylcholine acts as a synaptic transmitter in the preganglionic and postganglionic neurons of the autonomic nervous system. It is made up of choline and acetyl-CoA under the effect of choline-acetyltransferase. Acetylcholine has a variety of pharmacological effects such as slowing the heartbeat, expanding the arterioles and narrowing the bronchi. There are two types of acetylcholine (Ach) receptors: Muscarinic and nicotinic receptors. Muscarinic receptors inhibit the secretion of GABA released from the parvalbumin (PV) positive gamma-aminobutyric acid (GABA) ergic intermediate neurons. Nicotinic

receptors stimulate the GABAergic intermediate neurons stained with cholecystokinin. Thus, when a unique stimulus come, a phasic activity is ensured through the fine-tuning of the response of pyramidal cells[41]. Ach levels increase throughout the childhood, reach the highest levels in the preadolescent stage and then remain constant[42]. Recent studies have shown that they are associated with learning in the hippocampus[43].

Noradrenaline and adrenaline

Identified to be associated with cognitive functions, the response to stress, depression formation and substance dependence[44], norepinephrine (NE) is found in the brain stem, especially in neurons located in the locus coeruleus. Approximately 10 NE receptors have been identified, divided into two main families, mainly alpha and beta. It has been shown that axonal extensions of NE neurons, whose cell bodies form on days 12-14 of embryonic life in rats, are fully developed at birth. In the postnatal period, central adrenergic nerve endings have been found to show a developmental process in the form of growing towards the areas they would innerve by finding a path [45]. Similar to dopaminergic, serotonergic, cholinergic, and GABA-ergic receptors, adrenergic receptor concentrations are highest in monkeys during the first 2-4 months of life, followed by a plateau, which is then followed by a gradual decline towards the adult levels [46]. It is suggested that NE, thought to play a role in anxiety,

alertness, attention, learning and memory functions, is responsible for experience-dependent plasticity, especially in sensory cortical regions, along with Ach in brain development [47].

Glutamate

There are2 receptor groups of glutamate (GLU), which is the predominant stimulating neurotransmitter in the brain and forms near to half of all synapses in the forebrain[42]. Metabotropic receptors composed of a single protein work G-protein dependently. Metabotropic receptors have three subtypes, N-methyl D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainite. Ionotropic receptors composed of several subunits are actually ion channel formations[48]. AMPA and NMDA receptors are usually located in the same synapse. This is why glutamate can be transmitted through both receptors at the same time [49]. The rate of transmission associated with AMPA/NMDA ina synapse varies depending on the nature and developmental level of the synapse[50].

GABA (Gamma-aminobutyrate)

There are 2 groups of receptors to which GABA binds: GABA-A and GABA-B. The effect of GABA on pyramidal cells at the postsynaptic level is determined by the type of GABA-A receptor it binds to. GABA has neurotrophic effects on progenitor cells, excitatory neurons and glial cells

via GABA-A receptors [51,52]. GABA-A receptor is heteropentamer. Six different alpha subtypes of it have been defined. The alpha-1 subtype responsible for the sedative effects of benzodiazepines is present in approximately 85% of GABA-A synapses in the adult cerebral cortex and is found in all postsynaptic areas of pyramidal cells. The alpha-2 subtype GABA receptors, which are responsible for the anxiolytic effects of benzodiazepines, have a higher affinity for GABA and a faster onset of activation. Therefore, GABA transmission is more effective in alpha-2 containing synapses. The alpha-2 subtype is the most prevalent in the prenatal period, but the alpha-1 subtype becomes dominant in the postnatal period. This can be interpreted as a reduction in the efficacy and speed of GABAergic delivery in the axonal basal segments during postnatal maturation. The dorsolateral prefrontal cortex (PFC) in primates is one of the most studied regions because it shows the general cellular and connectional organization in neocortical regions. Here, GABA neurons have been found to form subgroups based on their molecular, electrophysiological and anatomical properties. GABA neurons can be classified according to the type of calcium binding protein, which they carry. These can be grouped as parvalbumin (PV), calbindin (CB), calretinin (CR) positive. Especially, the density of PV-stained axon tips has been found to increase during the postnatal development [53].

Neuroparasites

Parasites are living beings which survive on more advanced organisms and always give harm to them at different levels. Parasites can be distinguished as compulsive or facultative parasites according to their needs of the host organisms. Biological cycles, the tissues in which they are located, the forms and the routes of transmission vary widely, but all interact with the physiological mechanisms of the host organism. They can manipulate, stimulate or suppress the immune response in different ways. Although geographical differences and socio-economic variables lead to differences in prevalence values, they do not affect the pathogenicity and virulence of agents. In the mortality rates obtained, it is observed that the immune responses of hosts are adversely affected; such as secondary factors are on the front lines, like the increase in HIV seropositivity and treatment options that cause immunosuppression [54-56].

According to their development, protozoans with single cells and helminths with multiple cells and some arthropods are among the parasites that got medical importance.

Protozoans lead to serious clinical manifestations, especially in the presence of immune deficiency. Helmints cause damage and inflammation due to mechanical trauma as their volume is massive. Among the tissues where the parasites are located, there are also central nervous sys-

tem (CNS) tissues. Different clinical signs are observed in neuro parasitosis. Among the symptoms are cognitive and psychological problems as well as neurological findings. In parasites that are located to the brain tissue of humans, diffuse insufficiency, encephalopathy or development of epilepsy due to a direct intracerebral localization of the agent. In a screening study for people with active epileptic attacks, it was understood that they had an infection that settled in the CNS at some point in their lives.There are a number of mechanisms that parasites use to invade tissues of the central nervous system [54,57,58].

A Protective Anatomic Shield for Our One of the Most Important Systems: Blood Brain Barrier

As an anatomic structure the blood-brain barrier (BBB), is a multi-layered formation which regulates the transpassing of molecules and cells to maintain the homeostatic balance. These functions play a major role in sustaining a physiological environment to neurons and other cells of CNS. This structure consists of various layers and is selective permeable. Micro vascular endothelial cells of brain (BMECs) are the main component of BBB layers. Structures of BBB includes pericytes, astrocytes (the main supportive cellular group of CNS) and basal membrane. Some specific features of BMECs differ themselves from other endothelial cells of the organism. These differences are in large numbers, including high-level transendothelial electrical resistance and tight junctions that delay cell-to-cell flow. These differences are necessary

and also required for protection of CNS. The first difference is existence of tight junctions (TJs) located intercellularly. The second one is the absence of fenestrae, thus causing reduced levels of fluid- phase endocytosis and the last difference is enzymes and carrier-mediated transport mechanisms localized asymmetrically. Due to the selective permeability property, the endothelial cells forming the barrier express their influx and efflux carrier pumps themselves. One of the reasons is to protect the brain tissues from foreign xenobiotics. These carrier molecules include ATP-binding cassette family members and multiple drug resistance proteins (MRP 1-6) [59-61].

Despite the correct functioning of BBB, some pathogen microorganisms may pass through this barrier and spread the infection to CNS. These pathogens use three main mechanisms to cross. Besides, transcellular and paracellular or intercellular passing, pathogens may employ infected cells of immune system, mostly macrophages like ‘’Trojan horse” for bypassing the barrier. Transcellular crossing is preferred by bacteria like *Escherichia* coli and Listeria *monocytogenes,* fungi like *Cryptococcus neoformans* and viruses like West Nile virus. Research showed that *Trypanosoma* sp. uses paracellular penetration. İntracellular pathogens like viruses or some protozoal parasites will choose the “Trojan horse” way to bypass because they developed some mechanisms for protecting themselves against lysis inside the cytoplasm of phagocytic cells. HIV and *T.gondii* may be given as examples for using this route [62-64].

In the means of parasites, some factors derive from them or host cells to induce and facilitate the crossing the BBB. Parasite originated molecules are generally enzymatic in nature and take source from the organelles of protozoons. Common studies showed some examples on this type of factors within the invasion mechanisms of parasites *T.gondii* and *T.brucei*. One of the major antigenic structures of *T.gondii*, MIC2 (a component from parasite's micronemes) interacts with ICAM-1 of the host cell to initiate the parasite to cross the barrier of the monolayer at cell culture studies. Right alongside with this, *T.gondii* uses frequently the ''Trojan horse '' mechanism. For manipulating an easy way to induce phagocytic cells to pass over, parasite infected ones increase their motility and migration activity depending on CD11b integrin function; and also attracted to the infection site by parasite secreted cyclophilin 18 which interacts chemokine receptor CCR5. Another parasite, *T.brucei* synthesize and excrete the cysteine protease enzyme called brucipain to make BBB more permeabile to parasites; that establish a bond with protease activated receptors of host cells [65-67].

Researchers indicated that in the experimentations with these two parasites, some factors are host derived. The expression levels of adhesion molecules like ICAM-1, VCAM-1 and cytokine IFN-γ is upregulated during the infection of *T.gondii*. These molecules expedite the passage of infected leukocytes across the BBB. *T.brucei* is using the host derived molecules to make its way through

the barrier. An upregulation also occurs in the cells of immune system to increase the secretion of cytokines like IFN-γ, TNF-α and adhesion molecules like ICAM-1. A significant explanation specifies that this kind of actions appears to be similar to mechanisms of T cells at the time of inflammation. Studies which deficient lab mice for TNF-α is used shows that in the lack of this cytokine both inflammatory response and the numbers of parasites and T cells in the brain parenchyma decrease. Though not assisting the parasite to enter the CNS, a helmint disease called neurocysticercosis also obtains high levels of cytokines and adhesion molecules which may lead to an uncontrollable inflammation and damage to CNS tissues. This situation arises from disruption of BBB and allowing an influx of leukocytes into the brain [68-71].

Toxoplasmosis

The only parasite in the *Toxoplasma* genus, located under the Apicomplexan parasites, is called *Toxoplasma gondii*. Seroprevalence in the world is one of the highest values.

In those who have a healthy immune response, they often do not have a clinical sign. There are three forms seen in the life cycle; tachyzoites that grow rapidly in the host organisms, bradizoites that remain latent in the tissue cysts, and oocysts that complete the cycle through intestinal epithelial cells in the final hosts, the members of Felidae family.

In addition to eating raw and undercooked meat and meat products containing bradyzoites, the oocysts are often consumed with contaminated food and water [72].

As the *T. gondii* enters the central nervous system tissues, it uses various mechanisms to avoid immune cells that are mobile in the area and to pass through the blood-brain barrier. Although *T. gondii* does not observe high cellular specificity during a normal biological cycle, it prefers to reproduce in immune system cells such as macrophages and neutrophils. Inside these cells, they can pass into the blood-brain barrier using '' Trojan horse ''. Studies have shown that parasites in infected cells are more likely to pass through the tissue than inoculated free parasites. At this point, it is also important that tachyzoite protect itself from being degraded within the phagocytic cell. The tachyzoite of the *T.gondii* can pass through the tight junctions between the endothelial cells with rapid movements and overcome the barriers. During this mechanism, the parasite uses the actin- myocin engine, which is found in the cytoskeleton. Similarly, the same mechanism is used when passing intestinal epithelial barriers. In cell culture studies, if physiological conditions are maintained, tachyzoites can bind to endothelial cells, but not go between them. On the other hand, when the tachyzoites make paracellular transitions, they do not make bounds to endothelial cells.In recent years, a mechanism that has been discussed above is the so-called transcellular transition.In this mechanism, the host cell lyses, which is infected by

T. gondii, so that the parasite can replicate itself and then passes through to the other side of the barrier. The three mechanisms also occur with the tacitoid forms of the agent. In particular, the last mechanism emphasized the necessity of having a high level of parasitism in contact. At this point, the triggering of the inflammatory response and the emergence of bleeding foci to clear the debris of lysing cells, which would damage the nerve tissues of the host organism, is not observed in these mechanisms [73-76].

During active HIV infection, because of the number CD4 (+) T cells decrease to under 100 cells/µl, the parasite itself easily localized the CNS and diffuse all tissues. Sometimes individuals may get the infection before the existence of immunodeficiency, so on the bradyzoite forms locating inside the tissue cysts, rupture it and transform into active multiplying tachyzoites. Getting source from this, toxoplasmosis is one most significant death causes in HIV seropositive patients because of encephalitis condition. The lesions made by *T.gondii* is consisting three zones separating with layers. Central zone includes few parasites and coagulative necrosis foci. İntermediate zone contains usually immune cells of inflammatory nature with tachyzoites and also hypervascular. The outer zone is composed of encysted parasites. These lesions do not contain a real capsular structure. The necrotic foci and surrounding inflammatory area cause the damage of CNS tissues where the lesions are located. During radiological examinations or routine check- up, the lesions can mimic

some kind of neoplastic formations like CNS lymphoma or multiform glioblastoma. After antiparasitic treatment, the parasitemia level and density of lesions will decrease but at CNS healed zones may calcify and sustain a continuous mechanical irritation alongside with calcified lesions from congenital toxoplasmosis [77-80]

İnfection of *T.gondii* may alter some kind of behavioral changes of host and with chronic phase, the hormonal changes also occur. Mental health disorders are frequently correlated with toxoplasmosis. Depression, psychosis, and schizophrenia have been widely studied. Mechanisms of how the parasite develop an alteration for this kind of problems are still researched and complex. Basically, within two ways this may become an evaluation. Firstly, releasing of immune mediators that can induce a normal response, thus causing inflammation. This requires a controllable balance for inducing and suppressing the response. The other CNS infections that cause similar immune responses do not alter behavioral changes as sharp as *T.gondii*. A prominent evidence for change like this, for the circling the life cycle intermediate hosts act more amicable to the definitive host ; cats. This behavior is named ‘’fatal feline” attraction in mice. These alterations seen mostly the chronic phase of toxoplasmosis. The second way is changing the neurotransmitters. Recently findings observed an increase in dopamine turnover in chronically infected mice. Studies showed that this neurotransmitter is some kind of a requirement to the parasite for proliferating. Besides dopamine, glutamate signaling may also

change during toxoplasmosis. Extracellular glutamate rise and its transporter molecule GLT-1 in glial cells got a two-fold fall in the chronic toxoplasmosis. These molecules interact with each other and also regulate the immune response [81-84].

Cerebral Malaria

In humans, malaria is a protozoan parasitic disease that is transmitted through the ectoparasitic stings of mosquitoes of the genus Anopheles. It is known that humans now lead to five different types of malaria.

Plasmodium spp. With malaria parasites. *P. falciparum* (the species most commonly found in sub-Saharan Africa and having the mortal clinical indication), and *P. vivax* (species of our country), *P. ovale*, *P.knowlesi* (the species most recently detected in humans) cause malaria in humans. n the life cycle of malaria parasites, both the vector and the last mosquito, the Anopheles mosquito, are asexually proliferating, whereas the intermediate hosts, including humans, exhibit asexual proliferation. Basically, the biological cycle of malaria parasites begins by transferring sporozoite forms to female mosquitoes. Extraperitoneal schizogony is the primary cause of proliferation in hepatocytes, which are the liver parenchyma cells. Merozoites, which are involved in circulation by exploiting hepatocytes, initiate erythrocyte thyrosion by invading erythrocytes. In the erythrocytes, the merozoites, which are formed by the increase of nuclei in cytoplasm and

cleavage of cytoplasms, blast the host cell and confuse it again and provide a return to the host organism [85-89].

In each erythrocyte schizogony, a certain percentage of parasites turn into macrogametocytes and microgametocytes, and if the person is then inserted by another Anopheles mosquito, the gametocytes passing through the vein cause sexual reproduction to occur in the presence of a synapse in the cytoplasm. Molecular methods and rapid diagnostic kits are increasingly used in malignancy, but the most common and practically preferred method is the preparation of blood samples taken from the fingertip and preparation of thick-blooded preparations, followed by microscopic examination by one of the hematological centers, usually Giemsa. The most characteristic clinical symptom of the malaria tablet is the rising temperature, which varies within the period of time. After the rise of fever, sweating and general fatigue and malaise are seen.

Anemia occurs because it multiplies in erythrocytes and detonates them. The malaria effect seen in our country is called *P. vivax* as well as *P.ovale* 's fever table is called inverse malaria. *P.falciparum*, the heaviest strain, is a tropical malt. Unlike other malaria agents, the main two causes of malaria caused by *P. falciparum* are that they infect only certain erythrocytes of other malaria agents, but *P. falciparum* infects erythrocytes of all ages and produces about twice as many merozoites as the others during their schizogony [90-96].

Cerebral localization is one of the most severe clinical symptoms of *P.falciparum* malaria. Most mortal complication of malaria is this condition and caused by sequestration of parasites to vascular endothelial cells. Plasma leakage and production of inflammatory cytokines are the results of this binding. Due to the parasites locate inside erythrocytes, they redound the cyto adherance features of cells, so on they also, block the capillary circulation. Hypoxia and ischemia occur at zones where erythrocytes cluster around. One of the main causes of erythrocyte sequestration is binding of *P.falciparum* erythrocyte membrane protein 1 (PfEMP1) to adhesion molecules on the surface of the host cell. Infected cells also form clumps and rosettes which impair the circulation of microenvironment. Another characteristic of the *P.falciparum* is secretion of histidine rich protein II; nowadays used as a diagnostic marker especially at rapid card tests. Research shows that, themore of this protein produced, themo refacile the parasite breach the BBB [97-100].

Cerebral Amebiasis

Cerebral amebiasis is a rarely seen parasitic disease which is caused by common intestinal localized pathogen amoeba *Entamoeba histolytica* or one of the free living amoebas, *Naegleria fowleri, Acanthamoeba* spp. and *Balamuthia mandrillaris*. The incidence of cerebral amebiasis is %0, 7- 0,8 and usually seen in male patients. Disease can be classified according to parasites that is the etiologic

agent and clinical symptoms. Besides uncommon cerebral invasion of *E.histolytica*, granulomatous amebic encephelatis (GAE) and primary amebic meningoencephalitis (PME) caused by *Acanthomoeba* spp., *Balamuthia mandrillaris* and *Naegleria fowleri* respectively; to be seen with a little bit higher prevalence [101].

GAE is mostly an opportunistic infection which can occur any time of the year. Both pathogens may enter the host organism via skin lesions contacting contaminated soil or respirating cysts. Clinical symptoms of this parasitic infection are much more severe in the immunocompromised individuals, especially HIV(+) patients. Diabetes, chronic alcoholism and IV drug taking are also risk factors for emerging the symptoms. After primary exposure, these amoebae join the circulation and may invade different parts of the body but got a tropism for CNS. The symptoms are not specific and may have seen in many similar diseases. Typical features include some kind of behavioral changes, hemipharesis, aphasia, fever, seizures, cranial nerve dysfunction, headache, increased intracranial pressure and sometimes loss of consciousness. Diagnosis may done by serological methods that detect the specific antibodies secreted against parasites but radio- neuroimaging techniques could be helpful for making certain the diagnose. At some circumstances, the correct diagnose may achieve only under autopsy conditions [102-104].

Another disease made by free living amoebae is called PAM. Its etiologic agent is *N.fowleri*. This parasite is a

flagellated amoeba spread worldwide and lives mostly in warm water reservoirs and natural sources. The prevalence of the disease is very low but mortality is high because of aggressive and rapidly progressing nature of the agent. All around the world, the number of total cases are not known but approximately 300 cases have occurred. Transmission takes place, usually by the inhalation of contaminated water from nasal cavities, mostly during a swimming or bathing session. Young adults and elder people are much more effected and after exposure to the parasite, they may become a casualty within a week or 10 days. This disease may easily confuse with bacterial or viral meningitis or encephalitis because the lack of specific symptoms. Invasion route of the parasite is via the olfactory nerve and after passing the cribriform plate, they reach the olfactory bulbs. The trophozoite form of the parasite gives damage to the region where it invaded in the means of inflammatory response and causing hemorrhage. The lesions bring about by the parasite, located mainly at the orbitofrontal lobe, temporal lobe, hypothalamus, pons, medulla oblongata and upper part of the spinal cord. Due to the wide distribution of the parasite to the CNS, bitemporal and frontal headache, nausea, some behavioral changes, photophobia and neurological abnormalities. Diagnosis is done frequently by the examination of native or stained cerebrospinal fluid microscopically to detect the parasites [105-107].

Trypanasomiasis

African trypanosomiasis is an endemicsub-SaharaAfricanparasiticdisease. Especially seen in countries like Congo and Uganda. The parasite *T.brucei* got two sub species according to the first geographical region where they isolated; *T.brucei gambiense* (West African agent) and *T.brucei rhodesiense* (East African agent). Disease is spread by the bite of vector Tsetse flies. Due to the climatic changes, the distribution of these flies widens, so on the sleeping sickness caused by the parasites emerge. Besides the referred countries, these parasites seen very rarely. The form of the parasite in the host organism is called trypomastigotes, while tsetse fly feeds on a blood meal from infected host it changes to procyclic trypomastigotes. During life cycle, at the salivary glands of fly the infective form may emerge; metacyclic trypomastigote. Parasite within the bite region on the body of host organism, migrate from there and through blood and lymphatic circulation invade different body parts. At last localize at CNS. The parasite may alter and change the glycoproteins of its antigens on the surface of the membrane. Because of this, no healthy and permeable immune response could occur during trypanosomiasis [108-112].

Common symptoms like rash, lymphadenopathy, and fever are seen. Diagnosis of the sickness done by detecting the parasites in blood or cerebro- spinal fluid under microscopic examination. Molecular methods like PCR may

be useful, too. There is a significant difference about aggression of these parasites which the West African agent is indolent and take years to manifest but East African agent is much more aggressive and may cause life-threatening situations. The most prominent symptom of trypanosomiasis is somnolence and insomnia depending the malfunction of biorhythm. These may see at the chronic phase of the disease. Due to the neurological damage death may occur [113-115].

Neurocysticercosis

Neurocysticercosis is a parasitic disease which caused by localization of larvas of Taenia solium (also referred to as pork tapeworm) to the CNS. *Taenia solium* is a cestode helmint; mostly seen in pork consumer countries and low socio- economic regions on the world. Rarely seen in Europe and US, its rise as a public health problem may base on its distinct invasion of human tissues, especially tissues of CNS, as will be mentioned under this headline. The dimensions of adult helmint *T.solium* is 2,5- 5 m. in length and 0,4- 0,5 cm. in width, and also a segmented one as a characteristic feature of cestodes. It includes 700 to 1000 segments, which the last ones are gravid ones containing eggs. Gravid segments will spread out and/or break down during the defecation of an infestated host. After ingestion of eggs by consuming contaminated food or water, oncospheres hatch in the intestines of new host organism and start to penetrate the intestinal wall, then invade different body parts. Humans are both the intermediate and defini-

tive hosts for this organism but the whole complex life cycle will not occur at the body of human beings [116-120].

Larval form of this helmint is called *Cysticercus cellulose*, a vesicle shaped translucent organism which includes an invaginated form of scolex, named protoscolex and filled with a clear fluid. Its diameter varies 5 mm to 4 cm. The double row spiked scolex will pop out while attaching the host tissues for invasive strategies. After the invasion the primary larval stage develop a secondary form called cysticerci. Depending the exact region where the cysticercosis are located, there are many clinical forms of this disease. The most common type is parenchymal type, then subarachnoid or cisternal, intraventricular and mixed types follow. Parenchymal type divided within itself into four stages: vesicular, colloidal vesicular and granular nodular types are active forms of parasite but the fourth type nodular calcified stage is inactive. The activity depends on the viability of the larva and the width of the cyst capsule. Nodular calcified stage of the larva triggers no immune response and got no pathogenesis ability. Especially, encephalitic clinical symptoms and changes in behavior mainly occur at parenchymal and intraventricular type, via the cystic metastases and inflammatory granulomas due to the chronic immune response and mechanical irritation. Subarachnoid type is characterized with large and multiloculated cysts named racemose cysts; shaped like a grape bunch. This type is not as aggressive as oth-

ers but tend to bleed because of close contact to the well circulated regions [121-128].

Echinococcosis

Cystic echinococcosis or hydatid disease is a parasitic disease caused by the larval stages of *Echinococcus granulosus* or *Echinococcus multilocularis*. Infestation to CNS occurs rarely, approximately %2 percentage. Basically, there is two different types of clinical course fort his disease. Cystic echinococcosis and alvelolar echinococcosis caused by *E.granulosus* and *E.multilocularis* respectively. Because of the common effects of sheep to separation of parasite, its prevalence is higher in countries like Australia, New Zealand and some South American countries. Definitive host to *E.granulosus* is members of *Canidae* family, especially domesticated dog and for *E.multilocularis* is arctic and red foxes. Adult form of helmint is 2- 6 mm in length and 0,5- 0,6 mm in width and consisting three compartments. The last one is gravid and including eggs [129-133].

Cystic echinococcosis develops three layers when located inside the tissues of host organism. The fibrous profiled outer layer called pericyst, middle laminated layer called ectocyst and permeable layer for nutrient molecules called endocyst. The endocyst; the inner circle; also consists of smaller versions of cyst named daughter vesicles. These vesicles include protoscolices which got a capability

to develop a whole mature cyst, distributed to another organ or tissue inside the host [134-138].

Toxocariasis

Toxocariasis is a world-wide seen parasitic disease. Mostly, the etiologic agents are the nemotode helmints T*oxocara Canis* and *Toxocara Cati*. Definitive hosts are dogs and cats, respectively. Transmission to humans are usually accidental depending on ingestion of highly resistant eggs from contaminated soil, food or water. Because the source of infection is often soil, children especially who eat soil, got a higher risk for toxocariasis. The prevalence of parasitosis is a little bit higher at rural areas than city centers. After entering the intestinal tract, eggs hatch in the small intestine and then migrate to liver. On the route the larvas of the helmint causes a responsive inflammatory irritation. Spreading to CNS tissues is not a common route but may result in severe conditions [139-142].

Classical symptoms like fever, headache, lethargy and weakness are seen. Humans are hosts that blocks the lifecycle of the parasite. Always a self- limiting disease but sometimes mortality levels raises through migration to CNS or ocular tissues. This journey of the larva to distinct tissues is called visceral larva migrans. It could result in granulomas where it passes; like liver, lungs, kidneys, heart, brain or eye; because of uncontrollable inducing of inflammation. Ocular localization may mimic symptoms like some kind of neoplastic lesions which exist at ocular sphere like retinoblastoma. It may give damage to the op-

tic nerve and cause blindness. Neurologic and cognitive effects widen within a range of hyperactivity in children or teenagers to dementia in elders. Although the other localizations of visceral larva migrans have got no severe symptoms, the CNS localization mainly, connected with subtle cognitive clinical patterns. For the diagnosing the helmint any kind of fecal examination is useless because only the larval stage is present at the tissues of humans; the parasite show no development to the adult form except in the definitive hosts. Besides neuro- imaging the lesions, serologic tests for detecting antibodies at serum samples or directly determining the larva at cerebro-spinal fluid.

Interaction of the *Toxoplasma Gondii* Infection in the Host Organism

According to the findings obtained, it has been determined that about 25% of the total population just in the United States is infected with *T. gondii*, and in some regions this percentage is up to 95% [143]. *T. gondii* parasites, which have been detected from the strains cloned so far, are collected in 3 main groups as type I, type II and type III [144].

T. gondii tries to control the behavior of the intermediate host it has infected, in order to be able to settle into the cat family, the last host where it will complete its life cycle. Even though the mechanism of the T. gondii infection-induced behavioral change has not yet been fully understood, studies have provided us with some information in this direction. Previously published studies in the liter-

ature show that *T. gondii* influences behavior by affecting the transmission of neurotransmitter signals [143]. Studies in mice show that *T. gondii* infection increases potassium-induced dopamine release from dopaminergic cells by several orders of magnitude [143].

The present evidence suggests that *T. gondii* produces some proteins to capture the host cell [145]. ROP13, the most known of these proteins, dissolves readily in the cytoplasm of the host cell and activates the STAT3/6 signaling mechanism [145]. The STAT3/6 pathway is a naturally occurring inflammatory response to pathogenic infections [146]. The stimulation of this pathway by non-normal ways is also responsible for the ceasing of the programmed cell death, tumor formation and metastasis [146]. Indeed, previous studies in the literature have shown that *T. gondii* inhibits apoptosis in the host cellit has infected [147-149].

The Mechanism of Dopamine-*Toxoplasma gondii* Relation

A rapid increase in the number of dopamine metabolites occurs in chronic *T. gondii* infections in rodents, while the amounts of norepinephrine and serotonin drop [150,151]. In addition, it has been observed that *in vitro* dopamine reinforcement increases a amount of parasites [152]. Similarly, it has been observed that in mice and rats given dopamine antagonists, there is a decrease in behavioral changes due to parasite infection [153,154]. Recent findings indicate that there is no change in the amounts of

tyrosine hydroxylase, DOPA decarboxylase (DDC), or vesicular monoamine transporter (VMAT), indicating that the infection of the parasite affects the amount of catecholamines in the host [155].

Interesting findings have emerged, when the effects of different *T. gondii* strains on genes expressing neuropeptides have been examined on SK-N-MC, a human neuroepitheloma cell line [156]. According to this study, type I *T. gondii* directly affects the genes responsible for the expressions of dopamine, glutamate and serotonin neurotransmitters as well as PROK2 and TAC1 neuropeptides, while type III *T. gondii* affects the kynurenine pathway. Type II *T. gondii* has been shown to have no effect on gene expressions in the neurotransmitter system [157]. The reality these results put forward can be summarized as follows; while type I *T. gondii* infection is directly related to the elevation of dopamine levels [152], Type III *T. gondii* infection affects the kynurenine pathway from the main pathways of tryptophan metabolism, affecting the speed-determining step in dopamine synthesis [158].

As mentioned above, *T. gondii* intends to increase the amount of dopamine in the host cell, which it infected by tyrosine hydroxylase production [160]. It has been observed that in mice with AAH gene (responsible for the expression of tyrosine hydroxylase enzyme) removed, a decrease in the abilities of T. gondii parasite to infect cats, lower oocyst production, and less sporulation take place [161].

Another important point in *T. gondii* infection is how it affects neurotransmitters in different sexes. Studies in this area show that there are great differences between male and female mice. In acute *T. gondii* infection, serotonergic activity is increased in male mice, followed by a mild increase in noradrenergic system [162]. Based on previous studies [163], the rise in noradrenergic and serotonergic systems is responsible for the suppression of the active behavior. The observed decrease in mobility during the acute infection period may be due to this change in the neurotransmitter activity [162]. In the same study, an increase in the amount of HVA, which is dopamine metabolite in the acute phase in male mice, has also been observed [162]. Earlier studies done in the acute infection period have shown that novelty seeking in rodents diminishes in this period [164], whereas the movements increase rapidly and at short intervals [165]. In another study, the changes in the gene expression of male and female mice in the advanced stages of *T. gondii* infection have been determined according to sex [166]. It has been put revealed that in females, *T. gondii* infection causes changes in the expression of genes involved in the forebrain development, neurogenesis, and sensory and motor coordination (such as decreased expression of fatty-acid binding protein-7 and eyes absent homolog 1, increased expression of semaphorin 7A) [167]. In male mice, *T. gondii* infection has generally been shown to cause changes in gene expression associated with the sense of smell (such as a decrease in receptors for the sense of smell and D4 dopamine receptor, an increase in the expression of slit homolog 1) [166].

However, it has been determined that the attraction of cat odor increases only in female mice, while the expression of genes related to the sense of smell of male mice changes [166].In addition to this, unlike male mice, female mice have been found to have hyperactivity in open field tests [166]. These results suggest that there may be sex differences in the occurrence of neuropsychiatric diseases due to parasitic infection in humans.

The Mechanism of Serotonin and Indoleamine 2,3-dioxygenase (IDO) in Neuro-Parasitic Infections

The inflammatory response resulting from a developing infection in the brain can affect the cycle called "neurocircuit" by affecting the metabolic and molecular pathways directly affecting neurotransmitter systems. This results in problems such as motivation (anhedonia) – characterized by many neuropsychiatric disorders including depression –, avoidance and alarm (anxiety). To further emphasize molecular pathways, proinflammatory cytokines – known as Type 1 and Type 2 interferons (IFNs), interleukin-1β (IL-1β) and tumor necrosis factor (TNF) – reduce the usability/ability of the monoamine group neurotransmitters in the body, such as serotonin (5-HT), dopamine (DA) and noradrenaline (NE) by increasing presynaptic reuptake pump functions. This event also begins to occur with the reduction of the enzyme called mitogen-activated protein kinase (MAPK). When MAPK is reduced, monoamine synthesis is reduced so that a reduction in cytokine-

dependent oxidative stress-sensitive NO synthase (NOS) and nitric oxide (NO) production also occurs [167 168]. Several cytokines, including IFNy, IL-1β and TNF, reduce the monoamine precursors (Precursor) by activating the enzyme indoleamine2,3-dioxygenase (IDO), which is also the enzyme that separates tryptophan into kynurenine in the metabolism of serotonin. At this time, activated microglia cells (CNS macrophages) in the brain convert kynurenine to quinolinic acid (QUIN) [169 170].QUIN binds to the receptor called *N*-methyl-d-aspartate receptor (NMDAR).This receptor, called NMDAR, acts as a glutamate receptor [170,171].This cytokine-induced mechanism leads to the stimulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to excessive amounts of Glutamate release. Excessive amounts of glutamate release may lead to brain-induced neurotrophic factor (BDNF) depletion and excitotoxicity, particularly when bound to extrasynaptic NMDARs. This, as a result of inflammation on growth factors such as BDNF, leads to neuronal growth, neuronal integrity, neurological distress that may occur in the long term, ultimately affecting learning and memory [171,172].

In addition to lowering serotonin levels in the body, the kynurenine pathway results in the synthesis of multiple metabolites, which can have neurotoxic effects. These metabolites include 3-hydroxy-kynurenine (3-OH-KYN) as well as quinolinic acid. 3-OH-KYN shows its deleterious effects by increasing reactive oxygen species (ROS) in

the brain. This increase in ROS leads to oxidative stress and possibly neuronal apoptosis. ROS overproduction is associated with an increase in monoamine oxidase (MAO) activity, disrupts the monoamine levels in the brain and occurs in a depressive mood (as depression). Quinolinic acid is a potent N-methyl-D-aspartate (NMDA) receptor agonist. Overstimulation of these receptors causes neuronal damage by causing increased calcium flux to target neurons. The increased calcium flow to the cells may also cause the formation of ROS. Both metabolites have been found to be elevated in some neurodegenerative disorders such as Huntington's disease and Parkinson's disease [173,174].

The increase in IDO activity resulting from increased levels of inflammatory cytokines is the only way that the immune system affects the nervous system. For this reason, there are many mechanisms that have to be researched/will be researched, by which the immune system and the nervous system can affect each other. In recent years, the search for these mechanisms/pathways has been the foreground/discussed [175,176].

This area, which is developing and opens to exploration, has actually been discussed even years ago. Robert Ader, assumed the founding father of this medical paradigm [177], at the end of the 1970s, demonstrated the role of the immune system in influencing behaviors. Within this mentioned mechanism, an upregulated immune system has significant effects, including an increase in the

level of kynurenic acid, and these effects cause depressive behavior [177].

The indoleamine2,3-dioxygenase (IDO) is an enzyme found in the microglial cells of the nervous system. This enzyme, opened by pro-inflammatory mediators/cytokines, is responsible for the formation of kynurenine rather than serotonin in tryptophan. Inflammation activates microglia to release this enzyme. When activated, IDO takes serotonin precursor tryptophan down the kynurenine pathway. This kynurenine increases the tryptophan ratio and may reduce the synthesis of serotonin [174,175].

IDO also metabolizes 5-hydroxytryptophan (5-HTP) and serotonin to 5-hydroxyquinuramine. When the immune system is activated, it means that serotonin increases abundantly. A possible consequence of the shunting / suppression of tryptophan in the kynurenine pathway is the low levels of serotonin. In this case, as the IDO activity increases, low serotonin levels are associated with clinical symptoms such as depression, insomnia and anxiety, since there will be less tryptophan to make serotonin [172,174].

Tetrahydrobiopterin (BH4) is a necessary cofactor in the synthesis of monoamine neurotransmitters. BH4 is required to convert phenylalanine to tyrosine, tyrosine to L-DOPA and tryptophan to 5-HTP. However, BH4 is quite sensitive to oxidation and dihydroneopterin (XPH2) becomes irreversibly degraded. Under oxidative stress conditions, BH4 is rapidly destroyed and BH4-dependent

enzymes cannot function. Lower levels of monoamine may be seen as a result of the reduction in the amount of BH4 that can be used as a cofactor. When BH4 declines, the body may not convert precursors properly, because its enzymes cannot function without BH4. This may lead to lower monoamine levels such as dopamine, norepinephrine, epinephrine, and serotonin. Deficiencies in these neurotransmitters have been associated with numerous clinical complaints such as depression, fatigue, attention deficit, insomnia and anxiety. It is extremely important to understand the link between oxidative stress and the neurotransmitter. If these links have inflammation or oxidative stress that affects neurotransmitter levels, there is a potential to affect the response to the patient and the treatment [178].

Differences of *T. gondii* Infection According to Sex

T. gondii, a protozoan parasite, modifies the host behaviors. It changes the natural disgusting behavior against cat odor and becomes a favorite person for the actual host. But, the underlying mechanism is still unknown. The parasite to localize randomly causes a change in the host behavior. The differences in this localization may explain why the behavioral changes differ from one host to another. One of the most important factors affecting the behavioral change is the location where the parasite is localized and the number of parasitic cysts. There are contradictory studies of whether or not tropism of *T. gondii* exists for

specific regions of the brain. But recently, it has been identified as neurotrophic rather than tropism in the brain.

While the noradernergic system activity is increased in the females with acute toxoplasmosis, it is observed to slightly increase in also males in some brain areas. The level of dopamine increases in acute infected mice [179]. It is believed that the parasite may be changing behavior of the intermediate host, which has its cysts, in order to be a favorite hunt by the main host of T. gondii. It affects the natural defense mechanism in infected rodents and makes fearless to the hunter [180-183].

It has been reported that *T. gondii* influences people's personal characteristics positively or negatively [184,185]. Specific parasites affect intermediate host behaviors differently depending on sex [183,186]. However, the studies and explanations of this mechanism are insufficient. However, neurotransmitter changes and associations have been described by Stibbs et al. [187]in 1985, but the activities and natural defense functions of neurotransmitter systems in selected brain areas have not been analyzed in detail. Reactions to *T. gondii* infection in females and males require comparative studies. The effects of *T. gondii* on the monoamine system activity (dopamine, norepinephrine and serotonin) are evident in all brain regions in both the acute and chronic phase, with invasion of the brain and this system is related to natural defensive behavior, emotion, and motor and sensory stimulation. There is a need for studies on the female-male differences in these

systems and mechanisms. Parasitic infection often changes natural defensive behavior and locomotive activity.

They caused significant changes in both sexes in monoamine neurotransmitter systems. In infected females and males, there is a change especially in noradrenergic and serotonergic systems, compared to uninfected control mice. In male [188] and female [189] rats, this situation causes the typical acute immunological response. The functions of noradrenergic and serotonergic systems inhibit active behaviors [190]. Characteristic behavioral change reduces mobility and self-protection behavior. This change of behavior is called "sickness behavior". Hydrolases catalyzed in the rate-limiting step in dopamine biosynthesis [191] have been shown to cause dopamine metabolism to increase in neurons [191]. Damage to the protection mechanism of infected animals is thought to be related to the increase in the amount of dopamine in the cell with the incoming parasite. Infected male rats have been shown to be moderately attracted to cat odor [182]. Later, in a study done in humans, while cat odor smells very good to males with toxoplasma infection compared to the ones without, this is less in infected females [192].

T. gondii infection reduces disgust against cat odor in male rats. The closest mechanism related to the topic involves the interaction of gonadal testosterone and brain nonapeptide arginine-vasopressin. Both of these substrates are sexually dimorphic. It is exclusively expressed in males. It proves that there are no behavioral changes in the females. *T. gondii* infection has been shown to reduce

disgust to cat odor in female rats. This change is not accompanied by the steroid hormone change. The removal of gonads has no effect on the behavior change and is not dependent on arginine-vasopressin. Behavioral changes in female and male occur with non-analogous mechanisms, but this is not yet known [193].

Decreased disgust against cat odor in infected male rats [180,181] reflects the manipulation done by the parasites. Since the cat is the main host of the parasite, the infection increases the chances of cat to hunt under natural conditions, but this is a mechanism that has not yet been explained [194]. The neuroendocrine mechanism of behavioral change in the host has been extensively studied in male laboratory rats195 -198].Several hypotheses have been proposed regarding the infected males' loss of disgust to the hunter's odor [191,192,199,200].In men, *T. gondii* infection increases testicular testosterone [198,201]. This testosterone crosses the blood-brain barrier and causes hypomethylation of the arginine vasopressin gene in the medial posterior dorsal amygdala region [202]. These increase arginine-vasopressin production and cause behavioral changes [203,204].

The testosterone is predominantly male reproductive hormone and also is found in females in small amounts [205]. It has a transcription connected to the medial amygdala arginine-vasopressin testosterone with a similar mechanism [206-208]. *T. gondii* infection do not affect

serum, estrogen and progesterone levels in gonads-intact animals. *T. gondii* alters disgust in female rats, but is not dependent on ovarian steroids. In male rats, it increases the testosterone production from testicles [197].

Testosterone is also produced from ovaries and the adrenal gland. Synthesis of testosterone produced in ovaries is important in behavioral change. The disappearance of disgust to cat odor does not change in infected animals ovaries removed. In toxoplasma-infected females, the loss of disgust to cat odor still happens. A similar effect is seen in male rats, too [180,182]. Similar changes were found in infections caused by toxoplasma in female and male rats [209].

Conclusion

Dopamine is a neurotransmitter with variety effects both in the central nervous system and peripheral nervous system. Dopamine interacts with serotonin, other catecholamines and immune system due to has a very important role in parasitic infections. There are many intracellular, zoonotic parasites. These parasites migrate to many tissues when they enter the host organism and can settle in a wide variety of cells. When the host cell enters, effect gene expression and many enzyme and protein that effect some path way such as apoptosis, increased neurotransmitter release, and affecting some physiological processes, causing homeostasis disruption and cause diseases. The well-known knowledge of the evolutionary process

and life cycle of parasites will prevent many neuropsychiatric and neurodegenerative diseases.

Acknowledgment

This study is supported by The Scientific and Technological Research Council of Turkey (Tubitak) given project number as 115S223.

References

1. Lanska DJ. The history of movement disorders. Handb Clin Neurol. 2010; 95: 501-546.
2. Hornykiewicz O. Dopamine miracle: from brain homogenate to dopamine replacement. Mov Disord. 2002; 17: 501-508.
3. Roe DL. The discovery of dopamine's physiological importance. Brain Res Bull. 1999; 50: 375-376.
4. Chinta SJ, JK Andersen. Dopaminergic neurons. Int J Biochem Cell Biol. 2005; 37: 942-946.
5. Bisaglia M, Greggio E, Beltramini M, Bubacco L. Dysfunction of dopamine homeostasis: clues in the hunt for novel Parkinson's disease therapies. FASEB J. 2013; 27: 2101-2110.
6. Seamans JK, CR Yang. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol. 2004; 74: 1-58.

7. Goto Y, Lee YA, Yamaguchi Y, Jas E. Biological mechanisms underlying evolutionary origins of psychotic and mood disorders. Neurosci Res. 2016; 111: 13-24.

8. Amin F, M Davidson, KL Davis. Homovanillic acid measurement in clinical research: a review of methodology. Schizophr Bull. 1992; 18: 123-148.

9. Lodge DJ, AA Grace. Hippocampal dysfunction and disruption of dopamine system regulation in an animal model of schizophrenia. Neurotox Res. 2008; 14: 97-104.

10. Eiden LE, Schäfer MK, Weihe E, Schütz B. The vesicular amine transporter family (SLC18): amine/proton antiporters required for vesicular accumulation and regulated exocytotic secretion of monoamines and acetylcholine. Pflugers Arch. 2004; 447: 636-640.

11. McElvain JS, JO Schenk. A multisubstrate mechanism of striatal dopamine uptake and its inhibition by cocaine. Biochem Pharmacol. 1992; 43: 2189-2199.

12. Baumeister AA, MF Hawkins. The serotonin hypothesis of schizophrenia: a historical case study on the heuristic value of theory in clinical neuroscience. J Hist Neurosci. 2004; 13: 277-291.

13. Fiş NP, M Berkem. Development of neurotrans-

mitter systems and their reşections on psychopathology. Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Psychopharmacology. 2009; 19: 312-321.

14. Shields P, D Eccleston. Evidence for the synthesis and storage of 5-hydroxytryptamine in two separate pools in the brain. Journal of neurochemistry. 1973; 20: 881-888.
15. Marmaras V, N Mimikos. Enzymic formation of serotonin in mammalian blood platelets and red cells. Cellular and Molecular Life Sciences. 1971; 27: 196-197.
16. Abrahamsson PA, Wadström LB, Alumets J, Falkmer S, Grimelius L. Peptide-hormone-and serotonin-immunoreactive cells in normal and hyperplastic prostate glands. Pathology-Research and Practice. 1986; 181: 675-683.
17. Seuwen K, J Pouysségur. Serotonin as a growth factor. Biochemical pharmacology. 1990; 39: 985-990.
18. Buznikov GA, WH Lambert, JM Lauder. Serotonin and serotonin-like substances as regulators of early embryogenesis and morphogenesis. Cell and tissue research. 2001; 305: 177-186.
19. Moiseiwitsch JR, Raymond JR, Tamir H, Lauder

JM. Regulation by serotonin of tooth-germ morphogenesis and gene expression in mouse mandibular explant cultures. Archives of oral biology. 1998; 43: 789-800.

20. Pilowsky L, GF Busatto, M Taylor, DC Costa, T Sharma, et al. Dopamine D2 receptor occupancy in vivo by the novel atypical antipsychotic olanzapine—a123 IBZM single photon emission tomography (SPET) study. Psychopharmacology. 1996; 124: 148-153.

21. Pompeiano M, J Palacios, G Mengod. Distribution of the serotonin 5-HT 2 receptor family mRNAs: comparison between 5-HT 2A and 5-HT 2C receptors. Molecular Brain Research. 1994; 23: 163-178.

22. Uzbay IT. [New pharmacological approaches to the treatment of schizophrenia]. Turk Psikiyatri Derg. 2009; 20: 175-82.

23. Luchetti F, Canonico B, Betti M, Arcangeletti M, Pilolli F, et al. Melatonin signaling and cell protection function. The FASEB Journal. 2010; 24: 3603-3624.

24. Carrillo-Vico A, Lardone PJ, Alvarez-Sánchez N, Rodríguez-Rodríguez A, Guerrero JM. Melatonin: buffering the immune system. International Journal of Molecular Sciences. 2013; 14: 8638-8683.

25. Binkley SA. Circadian rhythms of pineal function in rats. Endocrine reviews. 1983; 4: 255-270.

26. Reiter RJ, Tan DX, Rosales-Corral S, Manchester LC. The universal nature, unequal distribution and antioxidant functions of melatonin and its derivatives. Mini reviews in medicinal chemistry. 2013; 13: 373-384.

27. Zhang HM, Y Zhang. Melatonin: a well-documented antioxidant with conditional pro-oxidant actions. Journal of pineal research. 2014; 57: 131-146.

28. Lieberman HR, Waldhauser F, Garfield G, Lynch HJ, Wurtman RJ. Effects of melatonin on human mood and performance. Brain research. 1984; 323: 201-207.

29. Krause DN, ML Dubocovich. Regulatory sites in the melatonin system of mammals. Trends in neurosciences. 1990; 13: 464-470.

30. Tan DX, Manchester LC, Hardeland R, Lopez-Burillo S, Mayo JC, et al. Melatonin: a hormone, a tissue factor, an autocoid, a paracoid, and an antioxidant vitamin. Journal of pineal research. 2003; 34: 75-78.

31. Lerner AB, JD Case, RV Heinzelman. Structure of melatonin1. Journal of the American Chemical

Society. 1959; 81: 6084-6085.

32. Arendt J. Melatonin: characteristics, concerns, and prospects. Journal of Biological Rhythms. 2005; 20: 291-303.

33. Markus RP, ZS Ferreira. The immune-pineal axis: the role of pineal and extra-pineal melatonin in modulating inflammation. Advances in Neuroimmune Biology. 2011; 1: 95-104.

34. Pontes GN, Cardoso EC, Carneiro-Sampaio MM, Markus RP. Injury switches melatonin production source from endocrine (pineal) to paracrine (phagocytes)–melatonin in human colostrum and colostrum phagocytes. Journal of pineal research. 2006; 41: 136-141.

35. Muxel SM, Pires-Lapa MA, Monteiro AW, Cecon E, Tamura EK, et al. NF-κB drives the synthesis of melatonin in RAW 264.7 macrophages by inducing the transcription of the arylalkylamine-N-acetyltransferase (AA-NAT) gene. PLoS One. 2012; 7: e52010.

36. Carrillo-Vico A, Calvo JR, Abreu P, Lardone PJ, García-Mauriño S, et al. Evidence of melatonin synthesis by human lymphocytes and its physiological significance: possible role as intracrine, autocrine, and/or paracrine substance. The FASEB Journal. 2004; 18: 537-539.

37. Hardeland R. Melatonin: signaling mechanisms of a pleiotropic agent. Biofactors. 2009; 35: 183-192.

38. Aparicio-Soto M, Alarcón-de-la-Lastra C, Cárdeno A, Sánchez-Fidalgo S, Sanchez-Hidalgo M. Melatonin modulates microsomal PGE synthase 1 and NF-E2-related factor-2-regulated antioxidant enzyme expression in LPS-induced murine peritoneal macrophages. British journal of pharmacology. 2014; 171: 134-144.

39. El-Sokkary GH, Omar HM, Hassanein AF, Cuzzocrea S, Reiter RJ. Melatonin reduces oxidative damage and increases survival of mice infected with Schistosoma mansoni. Free Radical Biology and Medicine. 2002; 32: 319-332.

40. Santello FH, Frare EO, dos Santos CD, Toldo MP, Kawasse LM, et al. Melatonin treatment reduces the severity of experimental Trypanosoma cruzi infection. Journal of pineal research. 2007; 42: 359-363.

41. Freund TF. Interneuron diversity series: rhythm and mood in perisomatic inhibition. Trends in neurosciences. 2003; 26: 489-495.

42. Herlenius E, H Lagercrantz. Development of neurotransmitter systems during critical periods. Experimental neurology. 2004; 190: 8-21.

43. Rangel-Gomez M, M Meeter. Neurotransmitters

and novelty: a systematic review. Journal of Psychopharmacology. 2016; 30: 3-12.

44. Aston-Jones G, S Foote, F Bloom. Norepinephrine. Neuropsychopharmacology: The Fifth Generation of Progress. American College of Neuropsychopharmacology. Philadelphia: Lippincott Williams & Wilkins. 2002; 47-57.

45. Jonsson G, H Hallman. Substance P counteracts neurotoxin damage on norepinephrine neurons in rat brain during ontogeny. Science. 1982; 215: 75-77.

46. Lidow MS, PS Goldman-Rakic, P Rakic. Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proceedings of the National Academy of Sciences. 1991; 88: 10218-10221.

47. Manunta Y, J-M Edeline. Noradrenergic induction of selective plasticity in the frequency tuning of auditory cortex neurons. Journal of neurophysiology. 2004; 92: 1445-1463.

48. Bethea TC, L Sikich. Early pharmacological treatment of autism: a rationale for developmental treatment. Biological psychiatry. 2007; 61: 521-537.

49. Nicoll RA, RC Malenka, JA Kauer. Functional comparison of neurotransmitter receptor sub-

types in mammalian central nervous system. Physiological reviews. 1990; 70: 513-565.

50. Liao D, NA Hessler, R Malinow. Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. Nature. 1995; 375: 400.

51. Nguyen L, Rigo JM, Rocher V, Belachew S, Malgrange B, et al. Neurotransmitters as early signals for central nervous system development. Cell and tissue research. 2001; 305: 187-202.

52. Barker JL, Behar T, Li YX, Liu QY, Ma W, et al. GABAergic cells and signals in CNS development. Perspectives on developmental neurobiology. 1998; 5: 305-322.

53. Lewis DA, Cruz D, Eggan S, Erickson S. Postnatal development of prefrontal inhibitory circuits and the pathophysiology of cognitive dysfunction in schizophrenia. Annals of the New York Academy of Sciences. 2004; 1021: 64-76.

54. Walker M, Kublin JG, Zunt JR. Parasitic central nervous system infections in immunocomprimised hosts: malaria, microsporidiosis, leishmaniasis and African trypanosomiasis. Clin Infect Dis. 2006; 42:115-125.

55. Graeff- Teixeira C, Da Silva AC, Yoshimura K. Update on eosinophilic meningoencephalitis and

its clinical relevance. Clin Microbiol Rev. 2009; 22: 322-348.

56. Nash TE. Parasitic diseases that cause seizures. Epilepsy Curr. 2014; 14: 29-34.

57. Vezzani A, Fujinami RS, White HS, Preux PM, Blümcke I, et al. Infections, inflammation and epilepsy. Acta Neuropathol. 2016; 131:211-234.

58. Ngugi AK, Bottomley C, Kleinschmidt I, Wagner RG, Kakooza-Mwesige A, et al. Prevalnece of active convulsive epilepsy in Sub- Saharan Africa and associated risk factors: cross-sectional and case-control studies. Lancet Neurol. 2013; 12: 253-263.

59. Kim KS. Mechanisms of microbial traversal of the blood brain barrier. Nat Rev Microbiol. 2008; 6: 625-634.

60. Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006; 7: 41-53.

61. Krishnan A, Soldati- Favre D. Breaching the wall for brain access. Microbiol. 2016; 14.

62. Greiffenberg L, Goebel W, Kim KS, Weiglein I, Bubert A, et al. Nteraction of Listeria monocytogenes with human brain microvascular endothelial cells: InlB-dependent invasion, long term intracellular

groeth and spread from macrophages to endothelial cells. Infect Immun. 1998; 66: 5260-5267.

63. Chang YC, Stins MF, McCaffery MJ, Miller GF, Pare DR, et al. Cryptococcal yeast cells invade tge central nrevous system via transcellular penetration of the blood brain barrier. Infect Immun. 2004; 72: 4985- 4995.

64. Grab DJ, Kennedy PG. Traversal of human and animal trypanosomes across the blood brain barrier. J Neurovirol. 2008; 14: 344-351.

65. Masocha W, Rothenberg ME, Kristennson K. Migration of African trypanosomes across the blood brain barrier. Physiol Behav. 2007; 92: 110-114.

66. Rougier S, Montoya JG, Peyron F. Lifelong persistence of Toxoplasma cysts: a questionable dogma? Trends in Parasitology. 2016; 1572.

67. Batra A, Tripathi R, Gorthi S. Magnetic resonance evaluation of cerebral toxoplasmossi in patients with the acquired immunodeficiency syndrome. Acta Radiol. 2004; 45: 212-221.

68. Smith B, Smirniotopoulos G, Rushing E. Central nervous system ifections associated with human immunodeciency virus infecton: radiologic-pathologic correlation. Radiographics. 2008; 28: 2033-2058.

69. Chang L, Cornford ME, Chiang FL, Ernst TM, Sun NC, et al. Radiologic- pathologic correlation: Cerabral toxoplasmosis and lymphoma in AIDS. AJNR J Neuroradiol. 1995; 16: 1653-1663.

70. Tedford E, McConkey G. Neurophsiological changes induced by chronic Toxoplasma gondii infection. Pathogens. 2017; 6: 19.

71. Mahmoudvand H, Ziaali N, Ghazvini H, Shojaee S, Keshavarz H, et al. Toxoplasma gondii infection promotes neuroinflammation through cytokine Networks and induced hyperalgesia in Balb/C mice. Inflammation. 2016; 39: 405-412.

72. Evans AK, Strassmann PS, Lee IP, Sapolsky RM. Patterns of Toxoplasma gondii cyst distribution in the forebrain associate with individual variation in predator odor avoidance and anxiety realted behaviour in male Long-Evans rats. Brain Behav Immun. 2014; 37: 122-133.

73. Cabral CM, Tuladhar S, Dietrich HK, Nguyen E, Mac Donald WR, et al. Neurons are the primary target cell fort he brain-tropic intracellular parasite Toxoplasma gondii. Plos Pathogens. 2016; 12.

74. Yarovinsky F, Zhang D, Andersen JF, Bannenberg GL, Serhan CN, et al. TLR11 activation of dendritic cells by a protozoan profilin-like protein. Science. 2005; 308: 1626-1629.

75. Yarovinsky F, Hieny S, Sher A. Recognition of Toxoplasma gondii by TLR11 prvents parasite induced immunopathology. J Immunol. 2008; 181: 8478-8484.

76. Mahmoud ME, Fereig R, Nishikawa Y. Involvement of host defence mechanisms against Toxoplasma gondii infection in anhedonic and despair like behaviours in mice. Infect Immun. 2017; 85: 7-17.

77. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webter JP, et al. The neurotropic parasite Toxoplasma gonii increases dopamine metabolism. Plos One. 2011; 6: e23866.

78. Newton CR, Preux PM, Singhi P. Parasitic disorders. Handb Clin Nuerol. 2013; 112: 1139-1152.

79. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, et al. Malaria. Lancet. 2014; 383: 723-735.

80. Sanjib Mohanty, Terrie E Taylor, Sam Kampondeni, Mike J Potchen, Premanand Panda, et al. Magnetic resonance imaging during life :the ket to unlock crebral malaria pathogenesis? Malar J. 2014; 13: 276.

81. Millian JM, San Millian JM, Munoz M, Navas E, Lopez-Velez R. CNS complications in acute malaria: MR findings. AJNR Am J Neuroradiol. 1993;

14: 493-494.

82. Cox FE. History of the discovery of the malaria parasites and their vectors. Parasit Vectors. 2010; 3: 1-5.

83. Restrepo C, Raut A, Riascos R, et al. Imaging manifestations of tropical parasitic ınfections. Semin Roentgenol. 2007; 42: 37-48.

84. Yusuf FH, Hafız MY, Shoaib M, Ahmed SA. Cerebral maaria: insight into pathogenesis, complications and molecular biomarkers. Infection and Drug Resistance. 2017; 10: 57-59.

85. Newton CR, Hien TT ,White N. Cerebral malaria . J Neurol Neurosurg Psychiatry. 2000; 69: 433-441.

86. Bakiwewa SM, Weiser S, Grey M, Heng B, Guillemin GJ, et al. Synergistic induction of CXCL10 by interferon-gamma and lymphotoxin alpha in astrocytes: possible role in cerebral amalria. Cytokine. 2016; 78: 79-86.

87. Mundra S, Parmar U, Shukla D. A prospective study to identfy the co-relation of a disease severity of complcated malaria and clinical outcome. Indian J Res. 2016; 4: 7.

88. Dondorp AM, Pongponratn E. Reduced microcirculatory flow in severe faciparum malaria : pathophysiology and electon-microscopic pathol-

ogy. Acta Trop. 2004; 89: 309-317.

89. Newbold C, Craig A, Kyes S, Rowe A, Fernandez D, et al. Cytoadhernece , pathogenesis and the infected red cell surface in Plasmodium falciparum. Int J parasitol. 1999; 29: 927-937.

90. MacPherson GGW ,White NJ, Looreesuwan S, Warrell DA. Human cerbral malaria: a quantitative ultrastructural analysis of parasitized erythocyte sequestration. Am J Pathol. 1985; 119: 385-401.

91. Pino P, Vouldokis I, Kolb JP, Mahmoudi N, Livage ID, et al. Plasmodium falciparum infected erythrcyte adhesion induces caspase activation and apoptosis in human endothelial cells. J Infect Dis. 2003; 187: 1283-1290.

92. Parija SC, Jayakeerthee SR. Naegleria fowleri: a free living amoeba of emerging medical importance. J Commun Dis. 1999; 31: 153-159.

93. Jain R, Prabhakar S, Modi M, Bhatia R, Sehgal R. Naegleria meningitis: a rare survival. Nuerol India. 2002; 50: 470-472.

94. Barnett ND, Kaplan AM, Hopkin RJ, Saubolle MA, Rudinsky MF, et al. Primary amoebic meningoencephelitis with Naegleria fowleri: clinical review. Pediatr Neurol. 1996; 15: 230-244.

95. Healy JF. Balamuthia amebic encephelitis: radiographic and pathologic findings. AJNR Am J Neuroradiol. 2002; 23: 486-489.

96. Sell JJ, Rupp FW, Orrison WW. Granulomatous amibic encephalitis caused by acanthomoeba. Neuroradol. 1997; 39: 434-436.

97. Inderjit Deol, Laura Robledo, Armando Meza, Govinda S Visvesvara, Russell J Andrews. Encephalitis due to a free living amoeba (B.mandrillaris) case report with literature review . Surg Neurol. 2000; 53: 611-616.

98. Krol- Turminska K, Olender A. Human infections caused by free living amoebae. Annals of Agricultural and Environmental Medicine. 2017; 2: 254-260.

99. Nash TE. Parasitic diseases that cause seizures. Epilepsy Curr. 2014; 14: 29-34.

100. Showler AJ, Wilson ME, Kain KC, Boggild AK. Parasitic diseases in travelers: afocus on therapy. Expert Rev Anti Infect Ther. 2014; 12: 497-521.

101. Gill D, Chatha D, Carpio OR. Imaging findings in African tyrpanosomiasis. AJNR am J Neuroradiol. 2003; 24: 1383-1385.

102. Grab DJ, Kennedy PG. Traversal of human

and animal trypanosomes across the blood brain barrier. J Neurovirol. 2008; 14: 344-351.

103. Masocha W, Rothenberg ME, Kristennson K. Migration of African trypanosomes across the blood brain barrier. Physiol Behav . 2007; 92: 110-114.

104. Kristennsonn K, Mhlanga JD, Bentivoglio M. Parasites and the brain: neuroinvasion, immunopathogenesis and neuronal dysfunctions. Curr To Microbiol Immunol. 2002; 265: 227-257.

105. Enanga B, Burhmore RJ, Stewart ML, Barrett MP. Sleeping sickness and the brain. Cell Mol Life Sci. 2002; 59: 845-858.

106. Villanueva MS. Trypanosomiasis of the central ervous system. Semin Neurol. 1993; 13: 209-218.

107. Sierra MM, Arroyo M, Torres MC, Ramirez Cruz N, Hernandez FG, et al. Extraparenchymal neurocysticercosis: demographic, clinicoradiological and inflammatory features. Neglected Tropical Diseases. 2017; 11.

108. O'neal SE, Flecker RH. Hospitalization frequency and changes for neurocysticercosis, United States, 2003-2012. Emerg Infect Dis. 2015; 21: 969-976.

109. Gabriel S, Johansen MV, Pozio E, Smit GS, Devleesschauwer B, Allepuz A, et al. Human migration and pig/pork import in the Europaen Union: What are the implications for Taenia solium infections? Vet Parasitol. 2012; 213: 38-45.

110. Singh A, Garg RK, Jain A, Malhotra HS, Prakash S, Verma R, et al. Toll like receptor-4 gene polymorphism in patients with solitary cysticercus granuloma. J Neurol Sci. 2015; 355: 180-185.

111. Carpio A, Fleury A, Hauser WA. Neurocysticercosis: Five new things. Neurol Clin Pract. 2013; 3: 118-125.

112. Carpio A, Romo ML. The relationship between neurocysticercosis and epilepsy: an endless debate. Arq Neuropsiquiatr. 2014; 72: 383-390.

113. Agnès Fleury, Esperanza Garcia, Marisela Hernández, Roger Carrillo, Tzipe Govezensky, et al. Neurocysticercosis.:HP10 antigen detection is useful for the follw up of the severe patients. Negl Trop Dis. 2013; 7.

114. Kimura- Hayama E, Higuera J, Corona Cedillo R, et al. Neurorcysticercosis: radiologic-pathologic correlation. Radiograpics. 2010; 30: 1705-1719.

115. Castillo M. Imaging of neurocysticercosis. Semin Roentgenol. 2004; 39: 465-473.

116. Rahalkar MD, Shetty DD, Kelkar AB, Kelkar AA, Kinare AS, et al. The many faces of cysticercosis. Clin Radiol. 2000; 55: 668-674.

117. Lucato LT, Guedes MS, Sato JR, Bacheschi LA, Machado LR, et al. The role of conventional MR imaging sequences in the evaluation of nuerocysticercosis: impact on charecterization of the scolex and lesion burden. AJNR Am J Neuroradiol. 2007; 28: 1501-1504.

118. Lift AW, Mohchyt T. Neurocysticercosis. Radiology. 1999; 211: 472-476.

119. Poeschl P, Janzen A, Schuierer G, Winkler J, Bogdahn U, et al. Calcified neurocysticercosis lesions trigger symptomatic inflammation during antparasitic therapy. AJNR Am J Neuradiol. 2006; 27: 653-655.

120. Fan CK, Holland CV, Loxton K, Barghouth U. Cerebral toxocariasis: Silent progression to neurodegenerative disaorders? Clin Microbiol Rev. 2015; 28: 663-686.

121. Horak P, Tummeleht L, Talvik H. Predictors and markers of resitance to neurotropic nematode infection in rodent host. Parasitol Res. 2006; 98: 396-402.

122. Xinou E, Lefkopoulos A, Gelagotti M, et al. CT and MR imaging findings in cerebral toxocara

disease. AJNR Am J Neuroradiol. 2003; 24: 714-718.

123. Quattrocchi G, Nicoletti A, Marin B, et al. Toxocariasis and epilepsy: systematic review and meta analysis. Plos Negl Trop Dis. 2012; 6.

124. Davidson RK, Romig T, Jenkins E, et al. The impact of globalisation on the distriution of Echinococcus multilocularis. Trens Parasitol. 2012; 28: 239-247.

125. Garret M, Herbsman H, Fierst S. Cytologic diagnosis of echinococcosis. Acta Cytol. 1977; 21: 553-554.

126. Ramadan NI, Abel Aaty HE, Mahmoud MS, El Nori A. An enzyme linked immunoelectrotransfer blot assay for diagnosing of human cystic echinococcosis. J Egypt Soc Parastol. 1999; 29: 849-857.

127. El Shamam O, Amer T, El Atta MA. Manetic resonance imaging of simple and infected hydatid cysts of the brain. Magn Reson Imag. 2001; 19: 965-974.

128. Tuzun M, Altınors N, Arda IS, et al. Cerebral hydatid disease CT and MR findins. Clin Imaging. 2002; 26: 353-357.

129. Lucato LT, Guedes MS, Sato JR, et al. The

role of conventional MR imaging sequences in the evaluation of nuerocysticercosis: impact on charecterization of the scolex and lesion burden. AJNR Am J Neuroradiol. 2007; 28: 1501-1504.

130. Gabriel S, Johansen MV, Pozio E, Smit GS, Devleesschauwer B, Allepuz A, et al. Human migration and pig/pork import in the Europaen Union: What are the implications for Taenia solium infections? Vet Parasitol. 2012; 213: 38-45.

131. Restrepo C, Raut A, Riascos R, et al. Imaging manifestations of tropical parasitic ınfections. Semin Roentgenol. 2007; 42: 37-48

132. Kristennsonn K, Mhlanga JD, Bentivoglio M. Parasites and the brain: neuroinvasion, immunopathogenesis and neuronal dysfunctions. Curr To Microbiol Immunol. 2002; 265: 227-257.

133. Smith B, Smirniotopoulos G, Rushing E. Central nervous system ifections associated with human immunodeciency virus infecton: radiologic- pathologic correlation. Radiographics. 2008; 28: 2033-2058.

134. Smith B, Smirniotopoulos G, Rushing E. Central nervous system ifections associated with human immunodeciency virus infecton: radiologic- pathologic correlation. Radiographics.

2008; 28: 2033-2058.

135. Masocha W, Rothenberg ME, Kristennson K. Migration of African trypanosomes across the blood brain barrier. Physiol Behav . 2007; 92: 110-114.

136. O'neal SE, Flecker RH. Hospitalization frequency and changes for neurocysticercosis, United States, 2003-2012. Emerg Infect Dis. 2015; 21: 969-976

137. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, et al. Malaria. Lancet. 2014; 383: 723-735.

138. Sanjib M, Terrie ET, Sam K, Mike JP, Premanand P, et al. Magnetic resonance imaging during life :the ket to unlock crebral malaria pathogenesis? Malar J. 2014; 13:276.

139. Millian JM, San Millian JM, Munoz M, Navas E, Lopez-Velez R. CNS complications in acute malaria:MR findings. AJNR Am J Neuroradiol. 1993; 14:493-494.

140. Cox FE. History of the discovery of the malaria parasites and their vectors. Parasit Vectors. 2010; 3:1-5.

141. Restrepo C, Raut A, Riascos R, et al. Imaging manifestations of tropical parasitic ınfections.

Semin Roentgenol. 2007; 42:37-48.

142. Yusuf FH, Hafız MY, Shoaib M, Ahmed SA. Cerebral maaria: insight into pathogenesis, complications and molecular biomarkers. Infection and Drug Resistance. 2017; 10:57-59.

143. Prandovszky E, et al., The neurotropic parasite Toxoplasma gondii increases dopamine metabolism. PLoS One. 2011; 6: e23866.

144. Sibley LD, JC Boothroyd. Virulent strains of Toxoplasma gondii comprise a single clonal lineage. Nature. 1992; 359: 82-85.

145. Turetzky JM, Chu DK, Hajagos BE, Bradley PJ. Processing and secretion of ROP13: A unique Toxoplasma effector protein. Int J Parasitol. 2010; 40: 1037-1044.

146. Wang Y, van Boxel-Dezaire AH, Cheon H, Yang J, Stark GR. STAT3 activation in response to IL-6 is prolonged by the binding of IL-6 receptor to EGF receptor. Proc Natl Acad Sci U S A. 2013; 110: 16975-16980.

147. Goebel S, U Gross, CG Luder. Inhibition of host cell apoptosis by Toxoplasma gondii is accompanied by reduced activation of the caspase cascade and alterations of poly (ADP-ribose) polymerase expression. J Cell Sci. 2001; 114: 3495-

3505.

148. Nash PB, Purner MB, Leon RP, Clarke P, Duke RC, et al. Toxoplasma gondii-infected cells are resistant to multiple inducers of apoptosis. J Immunol. 1998; 160: 1824-1830.

149. Besteiro S. Toxoplasma control of host apoptosis: the art of not biting too hard the hand that feeds you. Microb Cell. 2015; 2: 178-181.

150. Mahmoud ME, R Fereig, Y Nishikawa. Involvement of Host Defense Mechanisms against Toxoplasma gondii Infection in Anhedonic and Despair-Like Behaviors in Mice. Infect Immun. 2017; 85.

151. Ihara F, Nishimura M, Muroi Y, Mahmoud ME, Yokoyama N, et al. Toxoplasma gondii Infection in Mice Impairs Long-Term Fear Memory Consolidation through Dysfunction of the Cortex and Amygdala. Infect Immun. 2016; 84: 2861-2870.

152. Strobl JS, Goodwin DG, Rzigalinski BA, Lindsay DS. Dopamine stimulates propagation of Toxoplasma gondii tachyzoites in human fibroblast and primary neonatal rat astrocyte cell cultures. J Parasitol. 2012; 98: 1296-1299.

153. Webster JP, Lamberton PH, Donnelly CA,

Torrey EF. Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite medication on Toxoplasma gondii's ability to alter host behaviour. Proc Biol Sci. 2006; 273: 1023-1030.

154. Skallová A, Kodym P, Frynta D, Flegr J. The role of dopamine in Toxoplasma-induced behavioural alterations in mice: an ethological and ethopharmacological study. Parasitology. 2006; 133: 525-535.

155. Tedford E, G McConkey. Neurophysiological Changes Induced by Chronic Toxoplasma gondii Infection. Pathogens. 2017; 6.

156. Xiao J, Li Y, Jones-Brando L, Yolken RH. Abnormalities of neurotransmitter and neuropeptide systems in human neuroepithelioma cells infected by three Toxoplasma strains. J Neural Transm (Vienna). 2013; 120: 1631-1639.

157. Ziegelbecker R. [Comment on the contribution: Nell, A., Steinhauser, G., Schiestle, W., Sperr, W.: Measuring fluoride content in drinking water in Vorarlberg]. Wien Klin Wochenschr. 1994; 106: 401-405.

158. Zi T Wang, Shiv K Verma, Jitender P Dubey, L David Sibley. The aromatic amino acid

hydroxylase genes AAH1 and AAH2 in Toxoplasma gondii contribute to transmission in the cat. PLoS Pathog. 2017; 13: e1006272.

159. Gatkowska J, Wieczorek M, Dziadek B, Dzitko K, Dlugonska H. Sex-dependent neurotransmitter level changes in brains of Toxoplasma gondii infected mice. Exp Parasitol. 2013; 133: 1-7.

160. Lin Y, Sarfraz Y, Jensen A, Dunn AJ, Stone EA. Participation of brainstem monoaminergic nuclei in behavioral depression. Pharmacol Biochem Behav. 2011; 100: 330-339.

161. Flegr J, Preiss M, Klose J, Havlícek J, Vitáková M, et al. Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite Toxoplasma gondii Dopamine, a missing link between schizophrenia and toxoplasmosis? Biol Psychol. 2003; 63: 253-268.

162. Gatkowska J, Wieczorek M, Dziadek B, Dzitko K, Dlugonska H. Behavioral changes in mice caused by Toxoplasma gondii invasion of brain. Parasitol Res. 2012; 111: 53-58.

163. Xiao J, Kannan G, Jones-Brando L, Brannock C, Krasnova IN, et al. Sex-specific changes in gene expression and behavior induced by chron-

ic Toxoplasma infection in mice. Neuroscience. 2012; 206: 39-48.

164. Zhu CB, Lindler KM, Owens AW, Daws LC, Blakely RD, et al. Interleukin-1 receptor activation by systemic lipopolysaccharide induces behavioral despair linked to MAPK regulation of CNS serotonin transporters. Neuropsychopharmacology. 2010; 35: 2510-2520.

165. Neurauter G, Schröcksnadel K, Scholl-Bürgi S, Sperner-Unterweger B, Schubert C, et al. Chronic immune stimulation correlates with reduced phenylalanine turnover. Curr Drug Metab. 2008; 9: 622-627.

166. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35: 702-721.

167. Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, et al. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to

CNS immune responses and depression. Mol Psychiatry. 2010; 15: 393-403.

168. Steiner J, Walter M, Gos T, Guillemin GJ, Bernstein HG, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflammation. 2011; 8: 94.

169. Miller AH, CL Raison. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016; 16: 22-34.

170. Sternberg JM, Forrest CM, Dalton RN, Turner C, Rodgers J, et al. Kynurenine Pathway Activation in Human African Trypanosomiasis. J Infect Dis. 2017; 215: 806-812.

171. Parrott JM, JC O'Connor. Kynurenine 3-Monooxygenase: An Influential Mediator of Neuropathology. Front Psychiatry. 2015; 6: 116.

172. Simone Formisano, Mady Hornig, Kavitha Yaddanapudi, Mansi Vasishtha, Loren H Parsons, et al. Central Nervous System Infection with Borna Disease Virus Causes Kynurenine Pathway Dysregulation and Neurotoxic Quinolinic Acid

Production. J Virol. 2017; 91.

173. Parlog A, D Schluter, IR Dunay. Toxoplasma gondii-induced neuronal alterations. Parasite Immunol. 2015; 37: 159-170.

174. Ader R, N Cohen. Behaviorally conditioned immunosuppression. Psychosomatic medicine. 1975; 37: 333-340.

175. Cook I, T Wang, TS Leyh. Tetrahydrobiopterin regulates monoamine neurotransmitter sulfonation. Proc Natl Acad Sci U S A. 2017; 114: E5317-e5324.

176. Gatkowska J, et al. Sex-dependent neurotransmitter level changes in brains of Toxoplasma gondii infected mice. Experimental parasitology. 2013. 133: 1-7.

177. Berdoy M, JP Webster, DW Macdonald. Fatal attraction in rats infected with Toxoplasma gondii. Proceedings of the Royal Society of London B: Biological Sciences. 2000; 267: 1591-1594.

178. Lamberton P, C Donnelly, J Webster. Specificity of the Toxoplasma gondii-altered behaviour to definitive versus non-definitive host predation risk. Parasitology. 2008; 135: 1143-1150.

179. Ajai Vyas, Seon-Kyeong Kim, Nicholas Gi-

acomini, John C Boothroyd, Robert M Sapolsky. Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors. Proceedings of the National Academy of Sciences. 2007; 104: 6442-6447.

180. Xiao J, Kannan G, Jones-Brando L, Brannock C, Krasnova IN, et al. Sex-specific changes in gene expression and behavior induced by chronic Toxoplasma infection in mice. Neuroscience. 2012; 206: 39-48.

181. Flegr J. Effects of Toxoplasma on human behavior. Schizophrenia bulletin. 2007; 33: 757-760.

182. Webster JP. Rats, cats, people and parasites: the impact of latent toxoplasmosis on behaviour. Microbes and infection. 2001; 3: 1037-1045.

183. Lindová J, Novotná M, Havlícek J, Jozífková E, Skallová A, et al. Gender differences in behavioural changes induced by latent toxoplasmosis. International journal for parasitology. 2006; 36: 1485-1492.

184. Stibbs H. Changes in brain concentrations of catecholamines and indoleamines in Toxoplasma gondii infected mice. Annals of Tropical Medicine & Parasitology. 1985; 79: 153-157.

185. Marek Wieczorek, Artur H Swiergiel, Hossein Pournajafi-Nazarloo, Adrian J Dunn. Physiological and behavioral responses to interleukin-1β and LPS in vagotomized mice. Physiology & behavior. 2005; 85: 500-511.

186. Pitychoutis PM, Nakamura K, Tsonis PA, Papadopoulou-Daifoti Z. Neurochemical and behavioral alterations in an inflammatory model of depression: sex differences exposed. Neuroscience. 2009; 159: 1216-1232.

187. Lin SY, Chang WJ, Lin CS, Huang CY, Wang HF, et al. Serotonin receptor 5-HT2B mediates serotonin-induced mechanical hyperalgesia. Journal of Neuroscience. 2011; 31: 1410-1418.

188. Elizabeth A Gaskell, Judith E Smith, John W Pinney, Dave R Westhead, Glenn A McConkey. A unique dual activity amino acid hydroxylase in Toxoplasma gondii. PloS one. 2009; 4: e4801.

189. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, et al. The neurotropic parasite Toxoplasma gondii increases dopamine metabolism. PloS one. 2011. 6(9): p. e23866.

190. Jaroslav Flegr, Pavlína Lenochová, Zdeněk Hodný, Marta Vondrová. Fatal attraction phenomenon in humans–cat odour attractiveness

increased for Toxoplasma-infected men while decreased for infected women. PLoS neglected tropical diseases. 2011; 5: e1389.

191. Abdulai-Saiku S, A Vyas. Loss of predator aversion in female rats after Toxoplasma gondii infection is not dependent on ovarian steroids. Brain, Behavior, and Immunity. 2017.

192. Worth AR, R Thompson, A Lymbery. Reevaluating the evidence for Toxoplasma gondii-induced behavioural changes in rodents. Adv. Parasitol. 2014. 85: e142.

193. Hari Dass SA, A Vyas. Toxoplasma gondii infection reduces predator aversion in rats through epigenetic modulation in the host medial amygdala. Molecular ecology. 2014; 23: 6114-6122.

194. House PK, A Vyas, R Sapolsky. Predator cat odors activate sexual arousal pathways in brains of Toxoplasma gondii infected rats. PloS one. 2011; 6: e23277.

195. Lim A, Kumar V, Hari Dass SA, Vyas A. Toxoplasma gondii infection enhances testicular steroidogenesis in rats. Molecular ecology. 2013; 22: 102-110.

196. Vyas A. Parasite-augmented mate choice

and reduction in innate fear in rats infected by Toxoplasma gondii. Journal of Experimental Biology. 2013; 216: 120-126.

197. Glenn A McConkey, Heather L Martin,Greg C Bristow, Joanne P Webster. Toxoplasma gondii infection and behaviour–location, location, location? Journal of Experimental Biology. 2013; 216: 113-119.

198. Vyas A. Extended epigenotype in a Rattus novergicus–Toxoplasma gondii association. Communicative & integrative biology. 2015; 8: e992743.

199. Auger CJ, Coss D, Auger AP, Forbes-Lorman RM. Epigenetic control of vasopressin expression is maintained by steroid hormones in the adult male rat brain. Proc Natl Acad Sci U S A. 2011; 108: 4242-4247.

200. Hari Dass SA, A Vyas. Copulation or sensory cues from the female augment Fos expression in arginine vasopressin neurons of the posterodorsal medial amygdala of male rats. Front Zool. 2014; 11: 42.

201. Hari Dass SA, A Vyas. Toxoplasma gondii infection reduces predator aversion in rats through epigenetic modulation in the host medial

amygdala. Mol Ecol.2014; 23: 6114-6122.

202. Goymann W, JC Wingfield. Male-to-female testosterone ratios, dimorphism, and life history—what does it really tell us? Behavioral Ecology. 2014; 25: 685-699.

203. Bluthe R-M, J Schoenen, R Dantzer. Androgen-dependent vasopressinergic neurons are involved in social recognition in rats. Brain Research. 1990; 519: 150-157.

204. Dantzer R, R Bluthe. Vasopressin involvement in antipyresis, social communication, and social recognition: a synthesis. Critical reviews in neurobiology. 1992; 6: 243-255.

205. Dantzer R, Koob GF, Bluthé RM, Le Moal M. Septal vasopressin modulates social memory in male rats. Brain research. 1988; 457: 143-147.

206. Skallová A, Kodym P, Frynta D, Flegr J. The role of dopamine in Toxoplasma-induced behavioural alterations in mice: an ethological and ethopharmacological study. Parasitology. 2006; 133: 525-535.