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Zinc–iron dysregulation and fear processing in chronic toxoplasma gondii infection: a ZFT-centered hypothesis

Abstract

Toxoplasma gondii is an obligate intracellular protozoan parasite capable of establishing lifelong infection in approximately one third of the global human population. While acute infection is typically asymptomatic in immunocompetent individuals, chronic toxoplasmosis has been increasingly associated with subtle neurobiological, behavioral, and neuropsychiatric alterations. Acute infection follows a 48–72hour tachyzoite replication cycle and can disseminate widely, particularly in immunocompromised hosts. Transmission occurs via ingestion of tissue cysts in undercooked meat, food or water contaminated with oocysts, or vertical (congenital) transmission. Standard treatment of acute toxoplasmosis includes pyrimethamine, sulfadiazine, and leucovorin, while spiramycin is indicated in pregnant women to reduce fetal transmission risk.

Experimental studies in rodents demonstrate parasite-induced disruption of innate fear responses, most notably the loss of aversion to predator odors ("fatal attraction"). Despite extensive documentation of these behavioral effects, the molecular mechanisms linking chronic infection to fear dysregulation remain incompletely understood. Evidence indicates that T. gondii infection disrupts host micronutrient homeostasis, particularly zinc and iron, alongside alterations in calcium signaling, antioxidant defenses, and hippocampal structure. This paper proposes a unifying hypothesis in which parasite-mediated sequestration of zinc and iron via a Zinc/Iron Transmembrane Transporter (ZFT) sustains chronic infection while indirectly destabilizing host neural circuits involved in fear learning and extinction.

Keywords: Toxoplasma gondii; acute toxoplasmosis; chronic toxoplasmosis; zinc deficiency; iron metabolism; calcium signaling; hippocampus; fatal attraction; micronutrients

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Introduction

Toxoplasma gondii is an obligate intracellular protozoan parasite capable of establishing persistent infections in humans and animals. Approximately one third of the global population harbors chronic infection.[1] The parasite's infectious cycle begins with ingestion of oocysts from cat feces or tissue cysts in undercooked meat. Once in the host, sporozoites or bradyzoites differentiate into rapidly dividing tachyzoites, completing intracellular replication every 48–72 hours.[2] Tachyzoites invade nucleated cells, replicate, and lyse host cells, disseminating throughout tissues including the brain, muscles, and retina. In immunocompetent hosts, acute infection is often mild or asymptomatic, but in pregnant women and immunocompromised individuals it can be severe.[3,4]

Transmission occurs via:

i. Ingestion of tissue cysts in undercooked meat (pork, lamb, venison)

ii. Consumption of food or water contaminated with oocysts shed by felines

iii. Vertical (congenital) transmission from mother to fetus during primary maternal infection

iv. Blood transfusion or organ transplantation (rare).[5,6]

Treatment of acute toxoplasmosis aims to limit tachyzoite replication and prevent dissemination. Standard therapy includes pyrimethamine, sulfadiazine, and leucovorin, with careful monitoring for hematologic toxicity. Pregnant women are treated with spiramycin to reduce vertical transmission; if fetal infection is confirmed, combination therapy after the first trimester may be indicated.[7,8]

Seminal animal studies revealed that chronic infection alters innate fear behavior, particularly aversion to predator odors ("fatal attraction").[9] Proposed mechanisms include parasite-driven alterations in dopaminergic signaling and modulation of host endocrine pathways.[10]

T. gondii also induces disturbances in host micronutrients and minerals. Clinical and experimental studies report reduced zinc, iron, magnesium, selenium, and antioxidant vitamins, alongside elevated intracellular calcium.[11,12] Calcium signaling is central for host neuronal plasticity and parasite motility, invasion, and egress [12,13]. Iron metabolism is disrupted through altered ferritin and transferrin pathways, leading to tissue-specific iron depletion, anemia, and ocular complications.[14]

Zinc depletion impairs fear learning and extinction, reduces immune competence, and alters hippocampal plasticity.[15–17] ZIP-family zinc transporters such as ZIP8 exert protective effects during acute infection.[16] Chronic zinc and iron deficiencies destabilize calcium signaling, reduce vitamin D3, vitamin E, and selenium availability, and impair antioxidant defenses, collectively contributing to hippocampal dysfunction and fear dysregulation.[17–21]

Hypothesis and conceptual framework

We hypothesize that chronic T. gondii infection is sustained, in part,

by parasite-mediated sequestration of host zinc and iron via a putative Zinc/Iron Transmembrane Transporter (ZFT). Persistent micronutrient depletion destabilizes calcium homeostasis, reduces antioxidant and vitamin-dependent defenses, and induces lasting structural and functional changes in the hippocampus. These convergent effects impair neural circuits governing fear learning, contextual memory, and extinction, providing a biologically plausible explanation for the fatal attraction phenomenon in chronically infected hosts.

Conclusion

Chronic Toxoplasma gondii infection is a unique model of parasite-driven neuromodulation. Behavioral alterations such as fatal attraction are well documented, but mechanistic understanding remains incomplete. Parasite-induced zinc and iron sequestration may sustain chronic infection while destabilizing calcium signaling, impairing antioxidant and vitamin-dependent pathways, and inducing hippocampal dysfunction. Clarifying parasite-mediated micronutrient transport could open novel avenues to mitigate neurobehavioral consequences of toxoplasmosis.

Ethical approval

This is a hypothesis-driven article; no human or animal subjects were involved.

Competing interests

The author declares no conflicts of interest.

Consent to publish

Not applicable.

Data availability

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