

***Toxoplasma gondii* and Schizophrenia: Linkage Through Astrocyte-Derived Kynurenic Acid?**

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Toxoplasma gondii is a ubiquitous food- and water-borne parasite that in most individuals is able to persist in multiple tissues, including the central nervous system (CNS), without causing an apparent clinical disease.¹ During the chronic phase of toxoplasmosis, the latent stage of the parasite is found in the CNS, and studies from murine models have established that long-term resistance to the parasite is dependent on the ability to generate and maintain parasite-specific CD4⁺ and CD8⁺ T cells. Consistent with this observation, patients with primary or acquired defects in T cell-mediated immunity are susceptible to toxoplasmic encephalitis (TE). Indeed, in patients with acquired immunodeficiency syndrome, *T. gondii* is one of the most common opportunistic infections affecting the CNS. One of the notable features that accompanies *T. gondii* infection in the CNS is a prominent activation of resident glial cells, in particular astrocytes.² We propose here that this event may play a causative role in the development of schizophrenia.

A considerable body of evidence links *T. gondii* infection to an increased incidence of schizophrenia.^{3,4,5,6} However, the association between the parasitic infection and disease, while strong, is so far exclusively correlative in nature. Based on epidemiological data, ie, statistical analyses, the hypothesis has with few exceptions ignored the cellular events and molecular mechanisms by which the infection might promote or precipitate pathophysiology associated with schizophrenia. Recent experiments in our laboratories have provided provocative clues regarding the enigmatic connection between infection and disease etiology.

Our collaboration originated from the central role that astrocytes play in the synthesis of kynurenic acid (KYNA), a metabolite of the kynurenine pathway of tryptophan degradation. When present at levels slightly above endogenous brain concentrations, this metabolite can inhibit both *N*-methyl-D-aspartate (NMDA) and α 7 nicotinic acetylcholine (α 7nACh) receptors.⁷ These two receptors are widely purported to have causative links to cognitive processes. Unrelated to antipsychotic medication, KYNA levels are significantly elevated in the brain of individuals with schizophrenia.⁸ Thus, it follows that abnormally high KYNA levels may contribute to the patients' cognitive impairment. This concept is supported by studies in rodents, which show that experimental elevation of cerebral KYNA levels results in impaired sensory gating.^{9,10} Furthermore, nanomolar concentrations of KYNA, by blocking presynaptic α 7nACh receptors on glutamatergic nerve terminals, have been shown to significantly reduce the extracellular levels of glutamate in rat brain *in vivo*.^{11,12} KYNA may thus contribute to the putative hyponicotinergic and hypoglutamatergic tone in schizophrenia.^{13,14}

In view of the proposed link between KYNA and cognitive processes, it is important to understand the biochemical events leading to and regulating its formation and function in the brain. KYNA synthesis is initiated by the oxidative ring opening of tryptophan by indoleamine 2,3-dioxygenase (IDO) and/or tryptophan dioxygenase (TDO). The reaction product of IDO and TDO, kynurenine, is then irreversibly converted to KYNA. In the brain, this transamination takes place almost exclusively in astrocytes, which then rapidly liberate newly produced KYNA into the extracellular milieu, placing the metabolite in an excellent position to influence surrounding neurons.¹⁵ Interestingly, the mRNA for tryptophan 2,3-dioxygenase (TDO2) is elevated in the brain of individuals with schizophrenia, and a concomitant increased density of TDO2-immunopositive astroglial cells is seen in the patients' white matter.¹⁶ Because TDO is one of the upstream enzymes responsible for the biosynthesis of KYNA, this enhanced expression could conceivably lead to an elevation of KYNA levels in the diseased brain and therefore play a part in the pathophysiology of the disorder.

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As noted above, astrocyte activation is a prominent feature of TE, but it was not known whether this reaction is associated with a dysregulation of KYNA production. In a first attempt to investigate this possible link, we recently examined the brains of chronically *T. gondii*-infected animals for signs of impaired kynurenine pathway flux. Indeed, infected mice showed massive astrocyte activation and, concomitantly, a greater than 7-fold increase in the brain content of KYNA.¹⁷ Because this effect was accompanied by an increase in the levels of KYNA's bioprecursor kynurenine, these changes are likely due to a stimulation of upstream kynurenine pathway enzymes such as IDO and/or TDO. At present, it is unclear whether this represents a direct response to invading parasites or, as seems more likely, a secondary consequence of the inflammatory response that accompanies the presence of *T. gondii* in the brain.

These results show that *T. gondii* infection provides an in vivo model system to modulate a biochemical pathway associated with schizophrenia. Jointly, the links between (1) *T. gondii* and schizophrenia; (2) *T. gondii* and astrocyte activation; (3) KYNA levels and schizophrenia; (4) KYNA synthesis and astrocytes; (5) KYNA, NMDA, and $\alpha 7$ nACh receptors; and (6) TDO2 and schizophrenia suggest the following hypothetical sequence of events: *T. gondii* infection, by activating astrocytes, increases KYNA formation in the brain. This effect is augmented in persons with elevated brain TDO activity, ie, individuals with a genetic predisposition for schizophrenia. Increased brain KYNA levels, in turn, cause or contribute to the excessive inhibition of glutamatergic and nicotiner-gic neurotransmission, which is believed to play an important role in the cognitive impairments seen in schizophrenia.

An interesting corollary of this hypothesis is that a reduction in cerebral KYNA formation might benefit individuals with schizophrenia by indirectly enhancing transmission through NMDA and $\alpha 7$ nACh receptors. This could be accomplished by timely interventions that attenuate or arrest the various consequences of the parasite infection¹ or, more specifically, by inhibitors of KYNA biosynthesis.¹⁸ The mouse model used in our study not only provides a convenient vehicle to test such interventions but will also allow further mechanistic insights into the links between toxoplasmosis and schizophrenia.

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