Neospora caninum infection of the nervous system, kynurenine pathway, and the parasitic pathway

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ABSTRACT

Neuroinflammation is a prevalent trait in virtually all neurological illnesses, making it one of the most researched areas in neuroscience. Although neuroinflammation's primary job is to defend the nervous system from an injury, the complicated and sequential response of activated glial cells can cause neurological damage. The inflammatory response can be neuroprotective, neurotoxic, or both depending on the kind of glial cell and the period after the injury. During neuroinflammation, numerous pathways are engaged, and several bioactive intermediates are produced. The kynurenine pathway, which catabolizes tryptophan and is involved in immunological control, neuroprotection, and neurotoxicity, is one of the most frequent. Various models have been utilised to investigate the kynurenine pathway metabolites' roles in the development and maintenance of inflammatory processes generated by infections. The parasite infection Neospora caninum, for example, might be utilised as a relevant model to investigate the involvement of the kynurenine pathway in the neuroinflammatory response and the fraction of cells participating. As the world's population ages, the prevalence of diagnosable neurological illnesses rises, indicating a negative impact on health and quality of life. Many investigations are being conducted to explore the possible roles of neuroinflammation in the aetiology of a variety of neurological illnesses. Although inflammatory processes may not cause such illnesses on their own, the immune system can have a significant impact on symptom severity and development. In such cases, scientists are currently exploring for therapeutic targets that might effectively reduce the increased immune responses associated with neuroinflammation.

Key Words: *Neuroinflammation*

PERSPECTIVE

In the Central Nervous System (CNS), neurons and glial cells construct complex and coordinated networks, one of which is to maintain homeostasis. Both astrocytes and microglia in the glia continually scan the CNS environment for possible injury. Astrocytes, in particular, have critical functions in maintaining the blood–brain barrier (BBB) integrity, regulating CNS metabolism, producing antioxidants and trophic substances, and engaging in synaptic transmission. Microglia, on the other hand, are thought to be the CNS's resident immune cells, contributing to the pro- and anti-inflammatory immune response by continually scrutinizing the brain parenchyma for metabolic waste, aberrant cells and proteins, infectious agents, and injured tissue.

Infections, traumatic or ischemic injuries, and toxic metabolite buildup are all known to cause disruption of brain homeostatic mechanisms. At early stages and/or lower degrees of activation, astrocytes and microglia (polarized as A2 and M2, respectively) can be neuroprotective, launching coordinated responses to restore homeostasis and prevent damage by quickly inducing acute inflammation. This might aid in tissue repair and neurogenesis, as well as the elimination of cellular waste, infectious agents, and aberrant proteins. These glial cells, however, can become neurotoxic and contribute to neurodegenerative processes when activated chronically and/or at high levels (polarized as A1 and M1).

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Researchers are still working to completely comprehend the molecular and cellular triggers for this functional flip, despite the fact that much has been reported.

The Kynurenine Pathway (KP), which produces a range of neuroactive metabolites, has been one of the most investigated in recent years. During neuroinflammation, the kynurenine pathway catabolizes approximately 95% of tryptophan, resulting in a significant decrease in serotonin and melatonin production and the generation of a slew of neurotoxic, neuroprotective, and immune-modulating molecules that play important roles in a variety of brain diseases.

Many studies emphasize the need of better understanding the complicated but coordinated glial response, as well as their important contacts with neurons in neuroinflammatory-implicated dysfunction. In this context, experimental models capable of simulating these interactions may provide fresh insights into the role of tryptophan metabolism in neuroinflammation. External variables such as infectious agents, for example, might possibly be exposed to in vivo animal models, ex vivo brain tissue slices, and in vitro freshly dissociated brain cells to acquire much-needed answers. Effective models, on the other hand, should allow for the detection and activation of astrocytes and microglia, as well as parasite persistence mechanisms that allow the infectious organisms to survive and proliferate.

As a result, infection with the parasite Neospora caninum looks to be a viable model for studying key neuroinfectious processes, and it may help to enhance knowledge of crosstalk pathways between neurons, astrocytes, and microglia. N. caninum is an Apicomplexa phylum obligate intracellular protozoan that produces cysts in the CNS and has been linked to miscarriages in cattle as well as neurological problems in dogs. As a result, the goal of this review is to highlight current information regarding the intricate relationships between neuroinflammation and the kynurenine pathway, as well as to address the importance of the N. caninum infection model.

Over the last three decades, the kynurenine pathway has been extensively investigated in the CNS, particularly in relation to its interactions with the immune system. Having stated that, the kynurenine pathway is very dynamic. Many CNS cell types, for example, have varied kynurenine pathway profiles according on the illness and location afflicted. During neuroinflammation, microglial activation happens swiftly and is marked by structural alterations from a putatively resting, surveilling, ramified cell to an active, spheroidal one (M1 type) releasing proinflammatory mediators such as cytokines. This M1 microglia also stimulates astrocytes, causing them to become reactive (A1 type). Many proinflammatory mediators, including cytokines (IL-1, IL-6, IL-12, IL-23, and TNF-), chemokines (CCL5 and CCL2), Adenosine Triphosphate (ATP), and reactive oxygen species (ROS), are released when these intercellular signals interact.

Induction of the regulating enzyme, Indoleamine 2,3, Dioxygenase 1 (IDO-1), is related with kynurenine pathway activation, and several proinflammatory mediators can enhance IDO-1 activity. This includes synergistic interactions between TNF-, IL-1, and IL-6, for example. Other research has found that IDO-1 induction can occur in monocyte/macrophage-like cells even in the absence of IFN-.

Following IDO-1, the activity of Kynurenine Mono Oxygenase (KMO), an enzyme primarily expressed in microglia that transforms kynurenine (Kyn) into 3-hydroxyanthranilic acid, is another critical step in the kynurenine pathway. The former affects macrophage apoptosis/necrosis pathways and possesses immunoregulatory and T-cell survival capabilities. The activation of KMO results in the production of Quinolinic Acid (QA).

Surprisingly, astrocytes do not express KMO, although microglia expresses all of the kynurenine pathway's enzyme components. Thus, activation of microglia by inflammatory mediators plays a critical role in boosting QA production. In homeostatic conditions, the generation of Kynurenic Acid (KA) by astrocytes partially counteracts the excitotoxic effects of QA generated by microglia via NMDA receptor antagonism. In inflammatory situations, astrocytes create a considerable quantity of Kyn, which microglia can take up and use as additional substrates to make QA. QA causes neurotoxicity by at least five separate pathways, including excitotoxicity via NMDA receptor activation, ROS production, and cytoskeletal instability. The imbalance in QA and KA synthesis, with QA buildup, amplifies the neurotoxic effects by inhibiting glutamate absorption by astrocytes. As a result, this mechanism cyclically drives ROS generation, disrupts the BBB, and increases phosphorylation of structural proteins including Tau, Neurofilament (NF), and Glial Fibrillary Protein (GFAP), resulting in cellular cytoskeletal instability.

Other kynurenine pathway catabolites show synergistic neurotoxic effects when combined with QA. We saw a reduction in neurite outgrowth and complexity after treating neuron cells with conditioned media produced from IFN-stimulated BV-2 microglia. We also found higher levels of tryptophan, Kyn, and 3-hydroxykynurenine (3-HK) in the conditioned medium. The neuronawfi 2l atrophy was completely avoided when the authors utilised kynurenine pathway inhibitors. Many researches have attempted to elucidate the involvement of astrocytes and microglia in neuroinflammation and neuroprotection, and each of the processes involved in neuroinflammation is still being studied. As previously stated, exposure to the Gram-negative bacterial lipopolysaccharide is a frequent technique to research neuroinflammation in cell culture and rat models. In vitro, LPS stimulates IFN- production, which results in the activation of IDO-1 and, as a result, the activation of the kynurenine pathway. Systemic LPS treatment has the same effect, promoting IDO-1 activity as well as the generation of TNF- and IL-6 in the brain.

Despite the efficiency of triggering neuroinflammatory processes, systemic LPS exposure has not fully clarified the mechanisms of kynurenine pathway. LPS injection can activate Pathogen-Associated Molecular Pattern Receptors (PAMPs), stimulating signaling pathways that lead to the generation of inflammatory cytokines. Nonetheless, the neuroinflammatory processes generated in the CNS by bacterial, viral, and parasitic infection appear to be significantly more dynamic than the more uniformed responses reported in response to LPS alone.

On the other hand, there are various neuroinfection models that use microbes such as HIV or Toxoplasma gondii. The N. caninum infection model is intriguing since it is not contagious to humans, making it a safer agent to utilize in medical research.

Furthermore, this parasite is simple to grow. Importantly, N. caninum can trigger neuroinflammatory processes, providing a feasible alternative method for studying brain cell connections and kynurenine pathway activity. This parasite is a member of the Apicomplexa phylum, which includes unicellular and spore-forming parasites. This group of parasites activates the immunological response, resulting in INF- generation, IDO-1 activation, and tryptophan depletion in host cells. Infection with these parasites also causes an increase in TNF- and IL-1 production. Infection with Apicomplexa parasites increases the synthesis of Kyn, 3-HK, and QA. Some results of N. caninum infection, including as Th2 cytokine production and neurotrophic factor release, may indicate an unusual immune response linked with parasite survival. These findings, however, should not be confused with general neuroprotection because infection progression causes astrocyte death and neurological damage. Other investigations have shown that the parasite may alter the immune response to promote its persistence, such as increasing the number of T CD8+ regulatory cells, inhibiting IL-12p40 production, and inhibiting Th1 response through STAT3 phosphorylation during the invasion phase. Taken together, these diverse immune responses to N. caninum infection highlight the model's utility in assisting in the identification and further characterization of the dynamic and context-dependent function of neuroinflammatory processes connected to the kynurenine pathway and ultimately, brain function in normal and dysfunctional conditions.