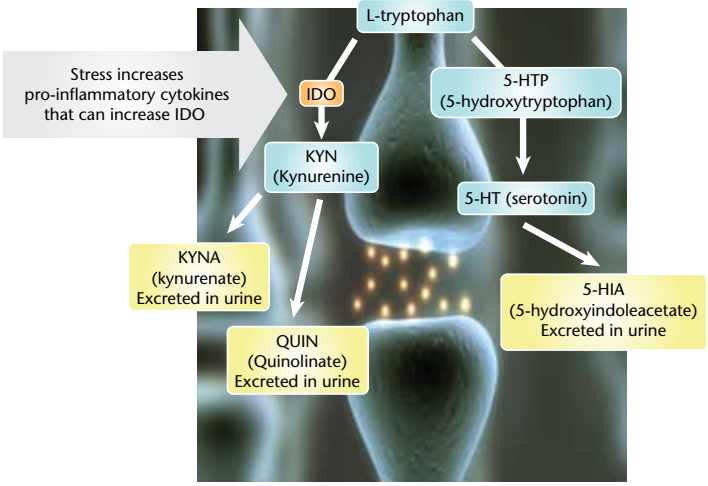
Important Markers of Neurological Inflammation: Kynurenate & Quinolinate

The kynurenine (KYN) pathway is a major route of L-tryptophan catabolism and operates as a mechanism of defense against intracellular pathogens and as a mediator of stress response signals to the brain.[1] Tryptophan can go down the KYN pathway and be excreted as kynurenate (KYNA) or quinolinic acid (QUIN), or it can be used to produce serotonin (5-HT) which is excreted as 5-hydroxyindoleacetate (5-HIA) [See Figure 1]. Depending on the timing and juxtaposition of signals, a balance between the neurotoxic and neuroprotective metabolites of KYN serve to either activate or inhibit neuronal responses.[2,3] The pathway leads to production of several neurobiologically active molecules. Among them is the excitotoxin QUIN which provides a critical link between the immune system and the brain. QUIN is known to be involved in the pathogenesis of several major inflammatory neurological diseases. Stimulation of the inflammatory response causes release of interferon-gamma (IFN-γ) by macrophages. There is a tight, positive association between QUIN and IFN-γ. QUIN can bind NMDA receptors of glutamatergic neurons that respond to pain and other peripheral signals. This biochemical event is the origin of typical pain symptoms in viral infections. If glutamatergic neurons are over stimulated, they can degenerate.[4] This degeneration has been noted in stroke, end stages of HIV infection, and Alzheimer's disease.

Figure 1



Toxicants can enhance sensitization of NMDA receptors, decreasing the threshold for which QUIN can induce neuronal loss. The widespread exposure to phthalates in plastic products has been shown to have potential for enhancing QUIN production.[5] Since the gut is frequently a source of chronic inflammatory signal induction via INF-γ, there is reason to suspect that QUIN elevation could indicate both inflammatory bowel conditions and neuronal degeneration. In inflammatory diseases, the ratio of QUIN/KYNA is frequently found elevated (> 2.0), so that neurotoxicity must be suspected.[6] This ratio can help to provide essential information about the pathway. Within the brain, the hippocampus is an area rich in NMDA receptors that is sensitive to the neurotoxic effects of QUIN.[7] These responses suggest that QUIN elevation is a metabolic event with the potential for precipitating brain developmental disruptions similar to that seen in regressive autism. Depression has been associated with immune activation and increased concentrations of pro-inflammatory cytokines, which have been found to affect the metabolism of brain serotonin. Tryptophan is catabolized to KYN by the enzyme indoleamine 2,3-dioxygenase (IDO), thus tryptophan supplementation may increase QUIN via the KYN pathway. It has been proposed that pro-inflammatory cytokines (IFNc, TNFa, IL-1, and IL-2) enhance IDO under stress which can promote the KYN pathway, thus depriving the 5-HT pathway of tryptophan and reducing 5-HT synthesis.[8] Thus, cytokine interactions can alter the balance between QUIN and KYNA supporting the link between stress and depression, as well as other diseases of inflammatory origin.[9-11] KYNA and QUIN can both be easily assessed in an Organix Profile. The Organix Profile is an excellent way to inquire about the cellular function of the inflammatory pathway, as well as monitor treatments that can affect the pathway.

References

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