

Organix™ Profile Pattern Analysis

Patterns of the Kynurenine Pathway

This communication is the first in a series that will highlight different patterns in the Organix™ markers of the **kynurenine pathway**, namely; **xanthurenate**, **kynurenate**, **quinolinate** and **picolinate**. Regardless whether or not biochemistry was your most loved subject at college or university you may not have heard of the kynurenine pathway. It is only in recent years that the pathway has emerged from relative obscurity to feature prominently in research associated with psychiatric disorders⁷ and regulation of the immune system.² The kynurenine pathway serves several purposes;¹

- a) Hepatic clearance mechanism for excess tryptophan
- b) Biosynthesis of nicotinamide (B3)
- c) Cell-mediated immune system regulation
- d) Biosynthesis of quinolinate for hippocampal regulation

Diverse Effects of Pathway Intermediates

Intermediates of the kynurenine pathway have diverse biological effects, with certain intermediates acting as neurotoxins, others as neuroprotective agents and still others as reactive oxidative species. Therefore, the relative balance of intermediates is important when interpreting patterns of the kynurenine pathway. The pathway also features an enzyme, kynureninase, which requires pyridoxal-5-phosphate as a co-factor. Thus, certain intermediates of the pathway also serve as functional markers of vitamin B6 sufficiency.

Factors Affecting The Kynurenine Pathway

B-vitamin deficiencies,¹ immune activation,² polyunsaturated fatty acid intake,³ phthalate exposure,⁴ protein intake,⁵ non steroidal anti-inflammatory drugs,⁸ and corticosteroids⁶ can all affect regulation of the kynurenine pathway. The cell-mediated (i.e., Th1-type) immune response is the most widely studied aspect of kynurenine pathway regulation. Th1 activation leads to release of interferon-gamma (IFN- γ) which induces the gate keeping enzyme, namely indoleamine 2, 3-dioxygenase (IDO), of the kynurenine pathway, leading to tryptophan degradation².

Kynurenine:Tryptophan Ratio – A Hallmark Immune Activation

The importance of the effect of cellular immune activation on the kynurenine pathway is underscored by the fact that many studies use the ratio of kynurenine to tryptophan as a marker of IDO activity. This ratio has been shown to correlate with the concentration of neopterin, another immune activation marker measured by Metamatrix (see Dec issues for more info). Infectious, autoimmune and malignant diseases that involve cellular (Th1-type) immune activation as well as pregnancy can lead to accelerated tryptophan degradation. Thus, for patients in states of persistent immune activation, markers of the kynurenine pathway provide a means for assessing and monitoring the development of immunodeficiency.

Impact of Immune Activation on Serotonin

A review of the diagram below allows one to see how the interplay of different factors affects the kynurenine pathway. Tryptophan is the initial substrate for both the kynurenine pathway and serotonin synthesis. Therefore, imbalances in an individual's immune system can affect the availability of tryptophan for serotonin synthesis and thus contribute to impaired quality of life and depressive mood.

Clinical Relevance of Kynurenine Pathway Markers

Each issue of this Organix™ Profile Pattern Analysis for the kynurenine pathway will present a case study that highlights a unique pattern of the kynurenine pathway and its clinical relevance with respect to treatment and symptoms.

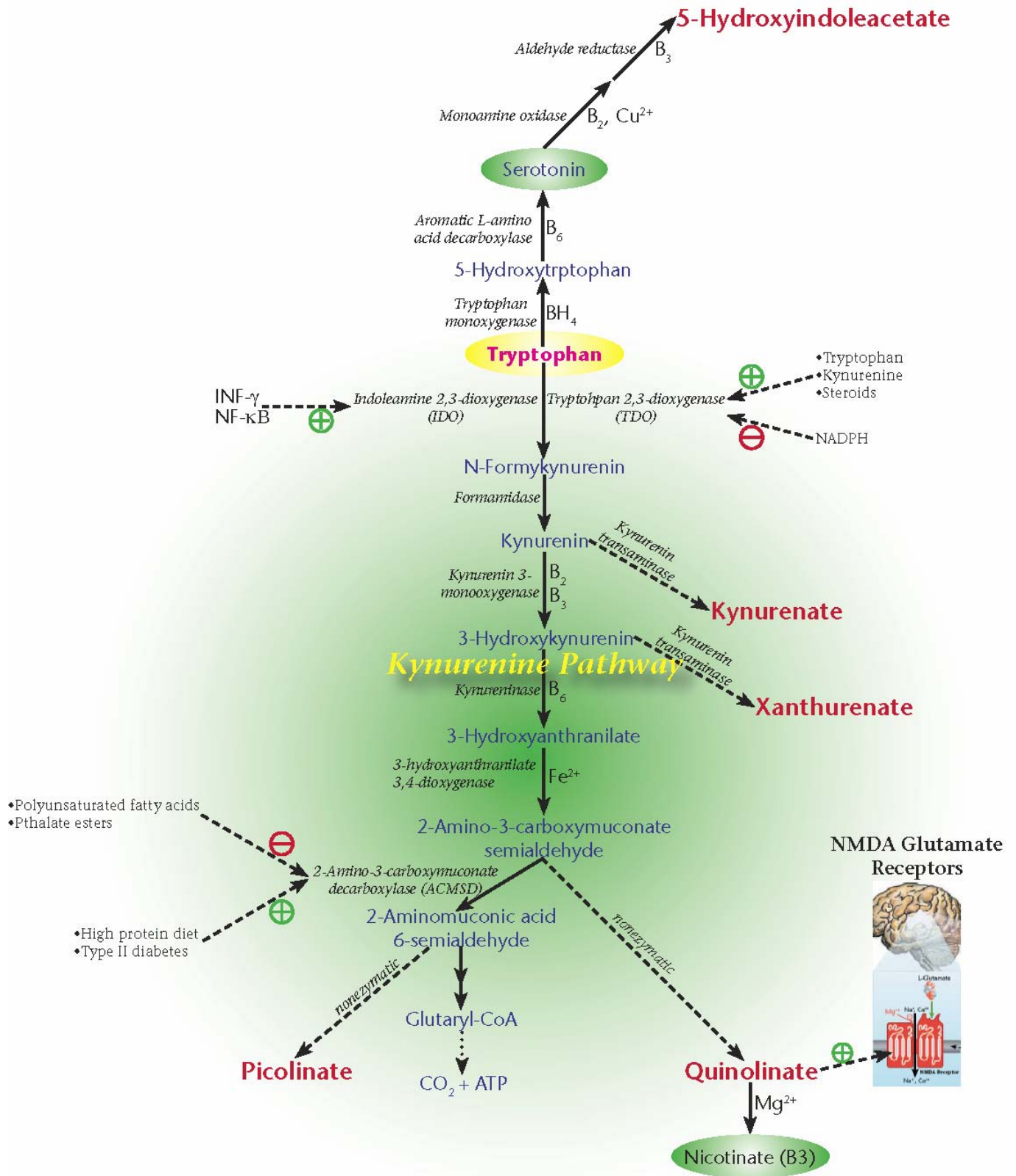


Figure 1. The figure shows the various intermediates and enzymes which make up the kynurenine pathway. Intermediary metabolites are featured in blue; makers which appear on the Organix™ Profile are featured in red, while key bioactive end products and intermediates are circled in green. Tryptophan is the starting amino acid from which metabolites of the kynurenine pathway are derived. Tryptophan also serves as the precursor for the synthesis of the neurotransmitter, serotonin and its breakdown product 5-hydroxyindoleacetate.

Pattern#1

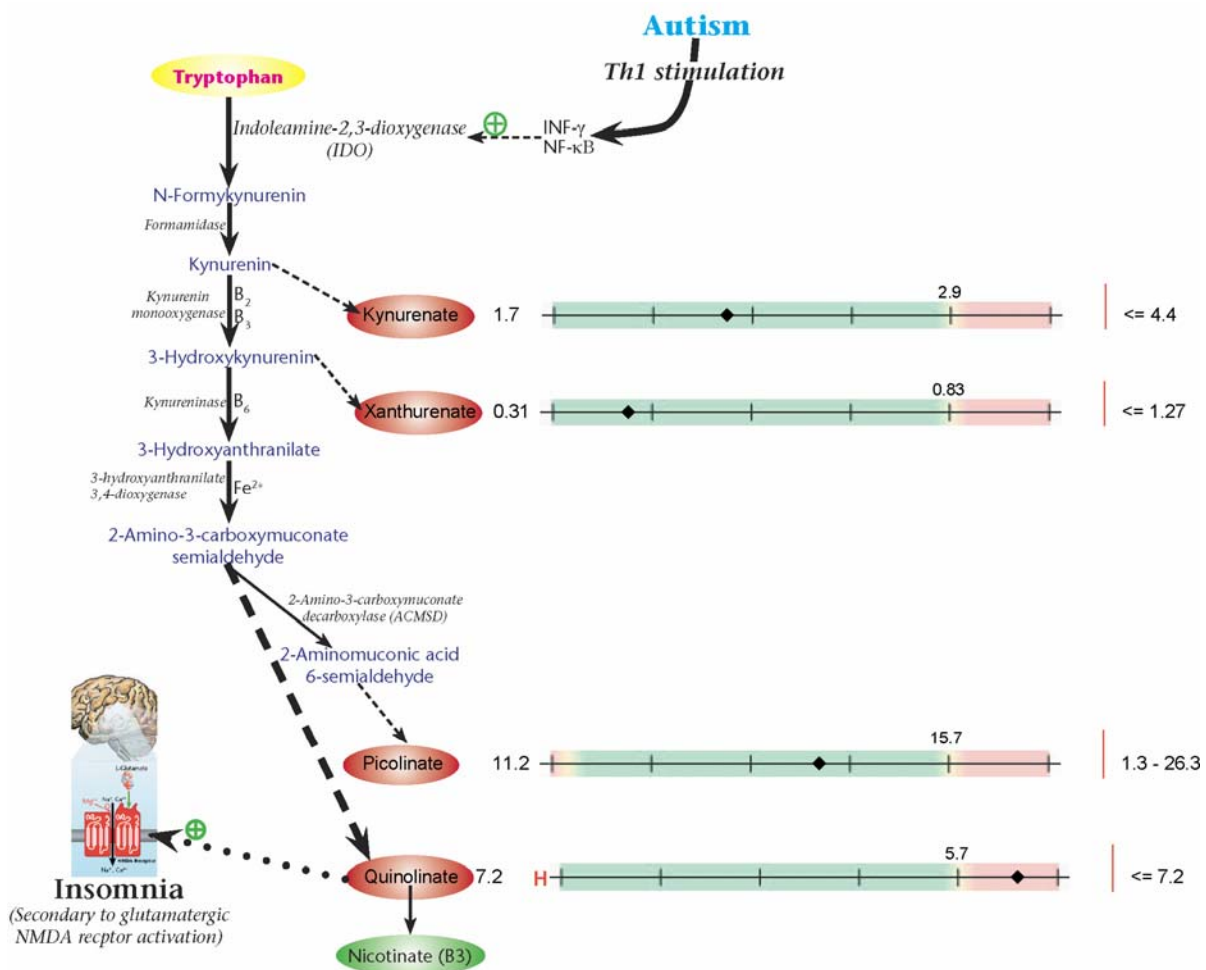
Single Quinolate Elevation

Patient: CB – 8 y/o M

Condition: Autism

Symptoms

- 'Chronic Fatigue' type reaction to immunization
- Poor attention
- Severe insomnia



Contrary to a recent ruling in the American federal "vaccine court" which rejected claims that either the measles/mumps/rubella (MMR) vaccine or thimerosal in vaccines caused children's autism (<http://www.medscape.com/viewarticle/588202>), the above case is an all too familiar scenario for a number of autistic children that present to integrative clinicians.

Concomitant with this patient's condition, activation of the Th1 immune response leading to raised quinolinate would provide a sound rationale to explain the patient's response to immunization and poor sleep. Quinolinate acts as an endogenous agonist of glutamatergic NMDA receptors, which can lead to poor sleep amongst other things. The excitatory stimulation of quinolinate is even more pronounced when there is no accompanying elevation of kynurenate which antagonizes the action of quinolinate.

Magnesium effectively competes for NMDA receptors so it would be an ideal supplement to give in this instance. An improvement in sleep quality would be evidence of magnesium's effect. Strategies to reduce immune activation, such as anti-inflammatory botanicals and removal of possible oxidative or toxic stressors would also be recommended.

References:

1. Stone TW. Kynurenines in the CNS: from endogenous obscurity to therapeutic importance. *Progress in Neurobiology*. 2001;64(2):185-218.
2. Schrocksnadel K, et al. Monitoring tryptophan metabolism in chronic immune activation. *Clinica Chimica Acta*. 2006;364(1-2):82-90.
3. Egashira Y, et al. Differential effects of dietary fatty acids on rat liver alpha-amino-beta-carboxymuconate-epsilon-semialdehyde decarboxylase activity and gene expression. *Biochimica Et Biophysica Acta*. 2004;1686(1-2):118-124.
4. Fukuwatari T, et al. Phthalate esters enhance quinolinate production by inhibiting alpha-amino-beta-carboxymuconate-epsilon-semialdehyde decarboxylase (ACMSD), a key enzyme of the tryptophan pathway. *Toxicological Sciences*. 2004;81(2):302-308.
5. Tanabe A, et al. Expression of rat hepatic 2-amino-3-carboxymuconate-6-semialdehyde decarboxylase is affected by a high protein diet and by streptozotocin-induced diabetes. *Journal of Nutrition*. 2002;132(6):1153-1159.
6. Shin M, et al. Regulation of mouse hepatic alpha-amino-beta-carboxymuconate-epsilon-semialdehyde decarboxylase, a key enzyme in the tryptophan-nicotinamide adenine dinucleotide pathway, by hepatocyte nuclear factor 4alpha and peroxisome proliferator-activated receptor alpha. *Molecular Pharmacology*. 2006;70(4):1281-1290.
7. Erhardt S, et al. The kynurenic acid hypothesis of schizophrenia. *Physiology & Behavior*. 2007;92(1-2):203-209.
8. Schwieler L, et al. Prostaglandin-mediated control of rat brain kynurenic acid synthesis--opposite actions by COX-1 and COX-2 isoforms. *Journal of Neural Transmission*. 2005;112(7):863-872.