NIADOXENE SELECT™ – A NEW PRODUCT THAT ADDRESSES A LITTLE KNOWN, UNDER APPRECIATED CONTRIBUTOR TO CHRONIC ILLNESS – DISTURBANCES IN TRYPTOPHAN METABOLISM PART II

In this final segment of this newsletter series on Niadoxene Select™, I will first finish the discussion about the impact of chronic inflammation on tryptophan and kynurenine metabolism and the decreases in serotonin and melatonin levels that often follow. Then I will discuss research on what we can do clinically to reduce abnormally increased IDO activity and optimize tryptophan and kynurenine metabolism in general with emphasis on the main constituents of Niadoxene Select™, vitamins B3 and B6.

SOME FINAL, “BIG PICTURE” THOUGHTS ON THE RELATION BETWEEN CHRONIC INFLAMMATION AND TRYPTOPHAN METABOLISM

Why, with chronic inflammation, would the body upregulate an enzyme that, on the surface, seems almost suicidal in nature?

The answer, as you might expect, relates to allostasis, the body’s total response to any stressor or accumulation of stressors, and allostatic load, where ill-health is the result of the allostatic stress response going on too long. Under normal circumstances the body wants to metabolize tryptophan to vitamin B3/NAD yet maintain optimal tryptophan levels so that serotonin and melatonin will be produced. In contrast, with inflammation the body actually wants to deplete tryptophan for a very good reason – to keep tryptophan away from other cells that require tryptophan such as bacteria and cancer cells. Schrocksnadel et al in their paper “Monitoring tryptophan metabolism in chronic immune activation” (Schrocksnadel K et al. Clinica Chimica Acta, Vol. 264, pp. 82-90, 2006) state the following:

“The pro-inflammatory cytokine IFN-gamma induces the enzyme IDO in a variety of cells. IDO activation limits availability of tryptophan. Because tryptophan is required for protein synthesis, withdrawal of this essential amino acid from the micro-environment arrests protein biosynthesis and subsequent growth of pathogens and proliferating cells. Consequently, tryptophan depletion is regarded as a defense mechanism induced by IFN-gamma in immunocompetent cells during immune response. This phenomenon acts as an antimicrobial or antitumoral effector mechanism and limits the growth of intracellular pathogens or malignant cells.”

Of course, with a short term stressor for which the allostatic response is optimally designed, IDO does its job to remove tryptophan and then is turned off before any damage is done. However, with long-term stress and chronic inflammation, which is epidemic in our society, the “good intentions” of the body become too much of a good thing, leading to, among other issues, loss of serotonin, melatonin, and, quite possibly, significant neurologic dysfunction and symptomatology.

Like every other cell in nature, immune cells that produce inflammatory cytokines require tryptophan.
If significant losses of tryptophan during chronic inflammation via the IDO-induced kynurenine pathway were not bad enough, tryptophan is also depleted in a massive way due to the fact that the inflammatory mediators involved in chronic inflammation also require tryptophan for their very existence. As I have mentioned in past newsletters, most of the inflammatory mediators involved in chronic inflammation are collectively called “acute-phase proteins.”

Reeds et al in their paper “Do the differences between the amino acid compositions of acute-phase and muscle proteins have a bearing on nitrogen loss in traumatic states?” (Reeds PJ et al. J Nutr. Vol. 124, pp. 906–910, 1994) point out how muscle experiences significant loss of tryptophan in order to supply this nutrient for the production of key acute-phase response inflammatory mediators:

“…four of the six proteins (C-reactive protein, amyloid A, haptoglobin, and α1-antitrypsin) contain a high content of phenylalanine, five of the proteins (C-reactive protein, fibrinogen, and α1-acid glycoprotein, haptoglobin, and amyloid A) are rich in tryptophan and three (α1-acid glycoprotein, haptoglobin, and amyloid A) contain high amounts of tyrosine.”

In addition, concerning muscle protein:

“…it is clear that if this is the major source of amino acids use in acute-phase protein synthesis, then, during the catabolic phase of the response to infection or injury, the demands for phenylalanine, tryptophan and tyrosine together necessitates the mobilization of an amount of muscle protein that is considerable in excess of the quantity of acute-phase proteins synthesized.”

Therefore, I hope you can see the following: With the chronic illness epidemic, which includes chronic inflammation; this makes serotonin and melatonin production from tryptophan a very low priority compared to production of inflammatory mediators and other factors that sequester tryptophan. So it should come as no surprise that we now have a vast population of people suffering from quality of life issues that relate to low serotonin and melatonin, particularly those that relate to CNS function and symptoms involving mood and attitude.

**WHAT CAN BE DONE TO ALTER CHRONIC INFLAMMATION INDUCED DESTRUCTION OF SEROTONIN AND MELATONIN AND REDIRECTION OF TRYPTOPHAN AWAY FROM SEROTONIN AND MELATONIN PRODUCTION?**

Traditionally, of course, for many years now our approach to treatment has been very limited. In terms of melatonin our only approach has been supplemental replacement. For serotonin, our only approach has been the use of herbs and pharmaceuticals that slow CNS metabolism so that the little serotonin that is available stays around longer. Now, research is clearly showing that we have a new and exciting way of looking at mood and neurologic dysfunction issues that involves optimization of chronic inflammation, IDO, and the kynurenine pathway. Allison and Ditor, in their paper “The common inflammatory etiology of depression and cognitive impairment: a therapeutic target” (Allison DJ & Ditor DS. J Neuroinflammation, Vol. 11, No. 151, 2014) state the following that reflects a whole new way of considering some of the most common clinical entities we face today that involve neurologic dysfunction:

“Both depression and cognitive impairment may share a closely linked inflammatory etiology stemming from a cytokine-induced imbalance in the kynurenine pathway. As this pathway provides the primary route for tryptophan (TRP) degradation, it plays a major role not only in the critical balance between neurotoxic and neuroprotective metabolites. As such a state of chronic inflammation, as is commonly reported in cases of depression and severe cognitive deficits, may contribute to the pathogenesis of each of these disorders.”
Consequently, the kynurenine pathway has become a prospective target for treatment interventions.”

With all that I have mentioned so far in this newsletter, and as suggested in the above quote, I now hope you can see that there are other options that focus not so much on preserving or adding to what little serotonin and melatonin is left after the ravages of chronic inflammation and IDO have taken their toll; but on both reducing chronic inflammation and optimizing tryptophan metabolism. Of course, you are all familiar with approaches on reducing chronic inflammation. Furthermore, I have written on this issue extensively in all the newsletters that have focused on allostatic load. Therefore, it is not my intention to discuss this aspect of treatment in this forum. However, there are also ways to optimize tryptophan metabolism independent of addressing the causational inflammation issue which might also have a significant impact on CNS dysfunction and behavioral issues. This is what I would like to focus on in the remainder of this monograph.

While many approaches have been discussed in the published literature, I would now like to focus on two that form the basis of the two active constituents in Niadoxene:

- **Reduction in IDO activity**
- **Optimization of a metabolite in the kynurenine pathway that is often produced in excess with increased IDO activity, xanthurenic acid.**

Niacinamide (vitamin B3) and reduction in IDO activity.

Recall from above that the end point of the kynurenine pathway is vitamin B3/NAD production. In a classic negative feedback manner, could administration of large amounts of niacinamide suppress IDO activity? Published papers suggest that this is a very viable clinical possibility.

Of course, from an historical perspective, it has long been known that gross deficiency of vitamin B3 is associated with numerous cognitive and behavioral abnormalities. Viljoen et al in their paper “Antidepressants may lead to a decrease in niacin and NAD in patients with poor dietary intake” (Viljoen M et al. *Med Hypotheses*, Vol. 84, pp. 178-182, 2015), state:

“Pellagra is characterized by photosensitivity, diarrhea, dermatitis and dementia. However, it is important to note that even in the absence of a diagnosis of pellagra, niacin deficiency may have effects on neuropsychiatric functions. Symptoms such as irritability, poor concentration, memory problems, anxiety, fatigue, restlessness, apathy, sleep disturbances, depression and dementia may result from niacin deficiency without it being recognized as such.”

With the above in mind, could niacinamide administration have an impact on neurologic function via IDO suppression? Schrocksnadel et al state:

“An alternative strategy is to increase the tryptophan pool via supplementation with niacinamide to suppress IDO activity. In patients with HIV infection, treatment with niacinamide was found to increase plasma tryptophan concentration by 40% with no major side effects. As such, administration of niacinamide might provide a valuable strategy to counteract tryptophan depletion by IFN-gamma-stimulated IDO in cells.”

In the above mentioned study, supplementation consisted of 3 g per day of niacinamide (niacinamide).

In the paper “Vitamin B3 for depression: Case report and review of the literature” by Prouskey (Prouskey JE. *J Orthomolecular Med*, Vol. 25, No. 3, pp. 137-147, 2010) the following is stated about the impact of niacinamide supplementation on tryptophan metabolism:

“Niacinamide…alters tryptophan metabolism to increase serotonin synthesis while limiting the formation of ‘kynurenines.’”

Vitamin B6 (Pyridoxal-5-phosphate-P5P-PLP), kynurenine metabolism, and insulin resistance

The role of the other active constituent in Niadoxene concerning kynurenine metabolism and mood disorders is a bit more complicated.
than that of niacinamide in that the role of P5P in Niadoxene Select™ relates more to its impact on insulin metabolism that a direct impact on IDO. However, the impact is just as important in terms of IDO activity since the chronic inflammation that drives increased IDO activity can either be created or upregulated by insulin resistance.

What you are about to see is research that suggests a very powerful vicious circle that involves P5P deficiency and persistent upregulation of IDO. What is happening? Basically, chronic inflammation will reduce P5P levels. In turn, deficiency of P5P leads to insulin resistance which then leads to more chronic inflammation. I realize that this may seem a bit confusing so let’s break it down to its individual parts.

The impact of inflammation on P5P

In the paper “Evidence for increased catabolism of vitamin B-6 during systemic inflammation” by Ulvik et al (Ulvik A et al. Am J Clin Nutr, Vol. 100, pp. 250-5, 2014) the following is stated about the impact of inflammation on vitamin B-6 metabolism:

“Plasma concentrations of PL 5’-phosphate (PLP), which is the active coenzyme form of vitamin B-6, are reduced during inflammation.”

In addition:

“A number of epidemiologic studies have shown reduced concentrations of circulating PLP in association with chronic or acute disease. Inverse associations have been shown between plasma PLP and the acute phase marker C-reactive protein (CRP) but also to a wider panel of inflammatory markers. Most evidence points to an altered tissue distribution as the main mechanism…”

However, the authors make it clear that the results of their study indicate that altered tissue distribution is not the only phenomenon taking place. Increased catabolism is also occurring:

“Broad-specificity enzymes upregulated to reduce oxidative and aldehyde stress could explain increased catabolism of vitamin B-6 during inflammation.”

What is the impact of P5P deficiency on IDO stimulated kynurenine metabolism?

To begin this discussion, please look again at the diagram from Part 1, also shown here:

At the metabolite 3-hydroxykynurenine there is a fork in the road. Some of the 3-hydroxykynurenine will proceed down to the production of 3-hydroxyanthranilic acid via the enzyme kynureninase, which uses vitamin B6 as a cofactor, and some will be sidetracked to the production of xanthurenic acid. Therefore, the amount of 3-hydroxykynurenine that goes down to form 3-hydroxyanthranilic acid versus the amount that is sidetracked to the production of xanthurenic acid is entirely dependent on the availability of P5P. Ideally, there would exist a balance between the two. In reality, though, since the entire pathway is being stimulated by chronic inflammation which, as stated above, depletes P5P, it is highly likely that too much xanthurenic acid will be produced. What is the impact of too much xanthurenic acid? As you can see from the diagram, excess xanthurenic acid can have a diabetogenic effect. Why is it diabetogenic? As you will see, xanthurenic acid has an adverse impact on insulin metabolism and, therefore, promotes insulin resistance. Then, if that were not bad enough, insulin resistance promotes chronic inflammation, thus, completing the vicious circle. With this basic overview in mind, let’s now consider the research.

In “Kynurenines and vitamin B6: link between diabetes and depression” by Oxenkrug et al (Oxenkrug G et al. J Bioinform Diabetes, Vol. 1, No. 1, November 12, 2014) the following is noted:
“Down-regulation of kynureninase, caused by P5P deficiency, shifts 3-hydroxykynurenine metabolism from formation of NAD to production of xanthurenic acid...”

How does increased xanthurenic acid lead to insulin resistance? In “Interferon-gamma-inducible kynurenines/pteridines inflammation cascade: implications for aging and aging-associated psychiatric and medical disorders” by Oxenkrug (Oxenkrug GF. J Neural Transm, Vol. 118, No. 1, pp. 75-85, January 1, 2012) the following is stated:

“Increased xanthurenic acid (XA) might contribute to the development of insulin resistance by formation of chelate complexes with insulin (XA-In). XA-In complex is antigenetically indistinguishable from insulin but its activity was 49% lower than activity of pure insulin. In addition, XA might exert toxic effect in isolated pancreatic islets because of formation of complexes with Zn\textsuperscript{2+}-ions in β-cells.”

Because increases in the kynurenine pathway induced by chronic inflammation are so closely linked with mood disorders such as depression and because kynurenine pathway upregulation powerfully reduces insulin sensitivity when vitamin B6 is depleted, Oxenkrug feels strongly that depression and diabetes are intimately linked:

“Combination of B6 deficiency in chronic inflammation with increased production kynurenine and 3-hydroxykynurenine in depression might contribute to the increased incidence of diabetes in depressed patients.”

Based in the above hypothesis, Oxenkrug et al in “Kynurenines and vitamin B6: link between diabetes and depression” suggest that reduction of the kynurenine pathway and optimization of vitamin B6 status might be an effective intervention concerning the development of diabetes in depressed patients and other conditions that might be related to vitamin B6 deficiency and inflammation-induced increases in kynurenine metabolism:

“Pharmacological down-regulation of the tryptophan-kynurenine-NAD pathway and maintenance of adequate vitamin B6 status might help prevent the development of diabetes in depression and other conditions associated with inflammation/stress-induced excessive production of kynurenine and vitamin B6 deficiency, e.g., obesity, cardiovascular diseases, aging, menopause, pregnancy, and hepatitis C virus infection.”

While the above mentioned conditions are complex and cannot be distilled down to a simplistic etiology that solely involves upregulation of kynurenine metabolism and vitamin B6 deficiency, I do feel that Oxenkrug makes a powerful case that addressing these two metabolic issues can have a major impact on improving quality of life in patients suffering from chronic inflammation induced mood and somatic ailments.

Based on the research I have presented, it appears that Niadoxene Select™ can have an impact on the key issues mentioned by Oxenkrug: upregulation of the kynurenine pathway and insulin resistance related to vitamin B6 deficiency.

**SOME FINAL THOUGHTS ON THE IMPACT OF CHRONIC INFLAMMATION ON NEUROLOGIC DYSFUNCTION INDUCED BY IDO-MEDIATED**
**Upregulation in Kynurenine Metabolism**

What you have just read, as complicated as it may seem, is merely an introduction to the massive amount of research on some of the most common mood and somatic chronic illnesses and how they are intimately related to reductions in CNS serotonin and melatonin caused by disturbed tryptophan/kynurenine metabolism. Furthermore, there also exists a very large body of research on the use of natural substances that can optimize the kynurenine pathway and thereby assist in the optimization of serotonin and melatonin levels. For me, what does this research suggest from a “big picture” standpoint? First, our arsenal to address serotonin and melatonin depletions which, as we all know, has traditionally been somewhat limited, questionably effective, and not without side effects, is now greatly expanded. Second, and maybe most importantly from clinical standpoint, knowledge of how chronic inflammation relates to the kynurenine pathway can be a “Rosetta stone” of sorts that will help us translate the mysteries of a whole host of clinical presentations relating to abnormal neurologic function into entities that are infinitely easier to understand and massively easier to address.

With the above in mind, for me, this newsletter and our first product that addresses inflammation-induced disturbances in the kynurenine pathway and the imbalances in serotonin and melatonin metabolism that inevitably follow, **Niadoxene Select™**, is just the beginning. In the future you are going to see many more newsletters that review the vast body of research on the kynurenine pathway as it relates to many different clinical manifestations of neurologic dysfunction. In addition, you will be seeing at least one additional product and maybe more that utilize many of the natural substances that can be used to address what I feel is one of the most ignored, under-appreciated, and misunderstood causes of neurologic dysfunction that exists today.

**Indications for Niadoxene Select™ Use**

**Laboratory findings on organic acids testing**
- Elevated xanthurenic acid
- Elevated kynurenine
- Elevated quinolinic acid

**Clinical presentation**
Signs and symptoms that would suggest a depressive state of mind.

**Niadoxene Select™ – Moss Nutrition**
Contents: 100 Vegetarian Capsules