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

PART I

INTRODUCTION

What you are about to read is the first of a two part series about our new product Niadoxene Select™. On the surface it appears to be deceptively simple with the active ingredients being just two nutrients – vitamin B3 in the form of niacinamide and vitamin B6 in the form of pyridoxal-5-phosphate (P5P, PLP). However, what I hope to convince you of in this two part series is that this very simple combination of nutrients is actually a therapeutic manifestation of a revolution in health care, particularly in relation to the epidemic of behavioral symptoms revolving around depressive states of mind, cognitive dysfunction, and neurologic imbalance in general.

In Part I of this series, I will highlight the somewhat complicated but important to know metabolic foundation for why Niadoxene Select™ is actually much more than what it appears to be if we judge the label using our usual body of knowledge concerning B vitamins.

DISTURBANCES IN TRYPTOPHAN METABOLISM: AN UNDER APPRECIATED, UNDER RECOGNIZED CAUSE OF CHRONIC ILLNESS

As we all know, the chronic illnesses experienced more and more by today’s patients have become more complicated both in terms of understanding and practical and cost effective management. Therefore, there has been a movement over the last 15 – 20 years to abandon the conventional philosophy that each illness is unique and different and adopt a philosophy that suggests that identifying underlying environmental stressors and metabolic imbalances that many, if not most, chronic illnesses share in common is the key to understanding and predictable, cost effective, and practical patient management. This philosophy, which has been eagerly embraced by the functional medicine community, suggests that understanding and addressing metabolic imbalances such as chronic inflammation, insulin resistance, and low-grade, chronic metabolic acidosis can lead to improved quality of life even for the most complicated chronic illness presentation. However, as most of you have come to realize, of all these metabolic imbalances, the one that seems to be the most important in terms of understanding and patient management is chronic inflammation.

Unfortunately, just identifying chronic inflammation and prescribing anti-inflammatory supplements and lifestyle recommendations is often not enough to assure a positive and predictable clinical outcome. Why? Inflammation, when it is present long term in chronically ill patients, can often have a complex ripple effect on human metabolism. This ripple effect often requires adjunctive interventions to address the individual “ripples” in addition to the usual anti-inflammatory approaches. Many of these ripples we do understand such as insulin resistance, low-grade, chronic metabolic acidosis, sarcopenia (loss of muscle mass), decreases in detoxification
enzymes, etc. However, there is one ripple that, despite a massive volume of published research that implicates it in a whole host chronic illness scenarios which include some very difficult to manage clinical presentations relating to behavioral disorders (such as depression and neurologic dysfunction), has been almost completely ignored and under appreciated by virtually everyone in both the allopathic and alternative medicine health care communities. What is this “ripple” that occurs largely as a byproduct of chronic inflammation?

Disturbances in tryptophan metabolism

These disturbances in tryptophan metabolism mainly involve increased production of a family of tryptophan metabolites collectively grouped under the term “kynurenine metabolites.” Niadoxene Select™ is the first of what we hope will be several products that we will be producing that are designed to optimize kynurenine metabolism and some of the detrimental clinical effects of kynurenine metabolism abnormalities. Of course, I would expect that many of you would assume that an issue as complicated as kynurenine metabolism would require an equally complicated product. In fact, as you will see, research suggests that the opposite is true. According to the research upon which it is based, Niadoxene Select™, a simple combination of niacinamide and vitamin B6 in the form of pyridoxal-5-phosphate, can be quite effective in contributing to the optimization of abnormal kynurenine metabolism.

Why would something as simple as a supplement containing vitamins B3 and B6 be effective in assisting in the optimization of kynurenine metabolism and, in turn, aid in quality of life improvement for some of the most difficult chronic illness patients? To answer this question, I will start at the beginning with some basics on tryptophan metabolism and how it is altered by chronic inflammation. Therefore, what first follows is a review of some key papers on disturbances in tryptophan metabolism with a focus on kynurenine metabolites and how imbalanced levels of these metabolites create ill-health and loss of quality of life. Then, in part II, you will see some papers that show how simple micronutrient supplementation with vitamins B3 and B6 can lead to significant improvements with certain chronic illness entities that have been demonstrated to have a particularly close association with disturbances in kynurenine metabolism such as behavioral disorders.

SOME BASICS ON TRYPTOPHAN METABOLISM

To begin to truly understand why disturbances in tryptophan metabolism can have such a profound impact on health in chronically ill patients, it is important to understand some basics. First, in a typical diet we ingest comparatively little tryptophan in relationship to other amino acids, as noted by Sidransky in the text Tryptophan: Biochemical and Health Implications (Sidransky H. CRC Press, Boca Raton, 2002, p. 3):

“Tryptophan is the least abundant amino acid in most proteins, accounting, on the average, for 1 to 1.5% of the total amino acids in typical plant (1%) and animal (1.5%) proteins.”

Because of the relative scarcity of tryptophan and the fact that, as I will describe shortly, it is required for so many important metabolic functions, there may not be sufficient quantities to support optimal health. Sidransky points out:

“…its supply may be insufficient for the normal functioning of the many pathways that depend on an adequate supply or level of tryptophan. One prominent view or belief has been that tryptophan, being present in low levels in proteins, is an important rate-limiting amino acid for many metabolic functions.”

What are these functions? Certainly most of us are aware of one – it is the precursor to serotonin. Furthermore, tryptophan is a precursor for melatonin by virtue of the fact that serotonin is converted to melatonin. However, as you will see, from a percentage standpoint, very little tryptophan is actually available for serotonin formation even under
ideal circumstances. Maehraj and Routy in their paper, “Tryptophan catabolism in chronic viral infections: Handling uninvited guests” (Mehraj V & Routy JP. *Int J Tryp Res*, Vol. 8, pp. 41-48, 2015) provide an overview of the many ways tryptophan is used in the body:

“Trp is metabolized into several downstream physiologically active substances, including serotonin, melatonin, nicotinic acid, and nicotinamide adenine dinucleotide (NAD).”

Before continuing, please note again in the above quote that one of the end products of tryptophan metabolism is vitamin B3 – nicotinic acid (a key component in NAD). Thus, unlike most of the other B vitamins, it is not a true essential nutrient – the body can make it.

The next extremely important point I want to make about tryptophan metabolism is that tryptophan is metabolized down two competing pathways. One of these pathways goes towards serotonin and melatonin and the other ends with NAD and nicotinic acid. However, as you will see shortly, before tryptophan is converted to nicotinic acid in this second pathway it is converted to several other key compounds that have a massive impact on health, particularly behavior and cognitive function. You will see shortly that chronic inflammation can cause significant imbalances of these tryptophan metabolites. Furthermore, as you will also see, *Niadoxene™* is designed to correct imbalances in these metabolites. More on that later. Before I discuss the intricacies of these two pathways, please note the diagram below from the paper “Interferon-gamma inducible kynurenines/pteridines inflammation cascade: implications for aging and aging-associated psychiatric and medical disorders” by Oxenkrug (Oxenkrug GF. *J Neural Trans*, Vol. 118, No. 1, pp 75-85, January 2011) that provides a pictorial overview of these pathways:

As you can see, the pathway that goes down towards NAD (niacin and nicotinic acid), which is the pathway that has the most significant impact on health in chronically inflamed, chronically ill patients, is quite complicated and involved. (Again, more detail on that later). For now, please note that the longer, downward pathway is described in the research papers I am going to discuss as “the kynurenine pathway” after the metabolite in the middle of this downward pathway.

From a percentage standpoint how much tryptophan goes towards the serotonin pathway as opposed to the kynurenine pathway? Given the importance of serotonin and its metabolite, melatonin, you might think that this amount is significant. Actually, the opposite is true. Very little goes towards serotonin production, and even less goes to the production of serotonin in the brain. In “Network beyond IDO is psychiatric disorders: Revisiting neurodegeneration hypothesis” by Myint and Kim (Myint AM & Kim YK. *Prog Neuro-Pharm Biol Psychiatry*, Vol. 48, pp. 304-313, 2014) the following is stated:

“Approximately 1% of the tryptophan available in the body is converted to serotonin, the synthesis of which takes place mainly in the enterochromaffin cells in the gut and 10 to 20% takes place in the brain after crossing the blood-brain barrier.”

Conversely, as noted by Oxenkrug from his paper quoted above:

“Approximately 99% of the dietary tryptophan, not used in protein synthesis, is metabolized along the kynurenine (KYN) pathway to produce nicotinamide adenine dinucleotide (NAD).”

Interestingly, even though tryptophan metabolism is heavily skewed towards the kynurenine pathway, in healthy individuals
production of serotonin and melatonin is great enough to assure optimal neurologic, behavioral and cognitive function. With chronic inflammation, though, this balance rapidly changes so that even less of the tryptophan goes towards the production of serotonin and melatonin. **Where does the tryptophan go instead?** As you will see, it increasingly goes down the kynurenine pathway and towards the production of inflammatory proteins.

To fully understand, though, how chronic inflammation can redirect the metabolism of tryptophan, it is important to know about the enzymes that catalyze these reactions. For, these are the entities that are actually affected by the inflammatory mediators. The first enzyme we need to talk about is the one that catalyzes the production of serotonin from tryptophan. This is tryptophan hydroxylase that actually catalyzes the conversion of tryptophan to a substance about which you are probably familiar, 5-hydroxytryptophan. However, two other enzymes are the most important to consider in terms of why the kynurenine pathway is upregulated during inflammation, why this upregulation causes problems clinically, and why **Niadoxene** is effective clinically. These enzymes are:

- **Indoleamine-2,3-dioxygenase (IDO)**
- **Tryptophan 2,3-dioxygenase (TDO)**

IDO, which is actually a family of two enzymes, IDO-1 and IDO-2, can be found in several different cell types throughout the body, as noted by Haroon et al in the paper “Psychoneuropsychosomatics meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior” (Haroon E et al. *Neuropsychopharmacology Rev*, published online September 2011):

> “Indoleamine-2,3-dioxygenase (IDO) is an enzyme expressed in multiple cell types, including macrophages, dendritic cells, microglia, astrocytes, and neurons.”

As I hope you can see, IDO is found in many different types of brain cells, which is not surprising given the relationship between upregulated IDO and neurologic disorders, which I will discuss in more detail. TDO, according to the paper mentioned above by Mehraj and Routy, is found in the liver, brain and cancer cells. Which enzyme is most dominant in terms of tryptophan and kynurenine metabolism? According to the paper by Myint and Kim mentioned above, under conditions of a healthy, low inflammatory scenario, TDO is predominant:

> “**Approximately 99% of tryptophan in the periphery is degraded in the liver by the enzyme tryptophan 2,3-dioxygenase (TDO) which is specific to tryptophan. In normal condition, the activity of TDO is mainly controlled by the tryptophan level itself and its activity is generally stable.**”

Therefore, you can see that with good health, tryptophan is metabolized by a classic negative feedback mechanism which is quite stable and poses a minimal threat to causing a disruption of good health. However, as you will see, with significant inflammation, this very stable situation drastically changes in two ways. The most important is a massive induction in IDO production, as pointed by Badawy in the paper “Tryptophan metabolism and disposition and utilization in pregnancy (Badawy AAB. *Biosci Rep*, published online September 17, 2015):

> “The extrahepatic pathway is controlled by another haemoprotein, IDO, the combined human tissue activity of which is normally, however, only 5-15% of that of hepatic TDO, but can be dramatically increased after immune activation by its principal effector IFN-gamma. The most remarkable feature of IDO is the astounding degree of its induction by IFN-gamma and agents acting through it under a variety of pathological conditions, which ranges between 20- and 4000-fold, rendering it the major player in the control of Trp availability under such conditions.”

Thus, with significant increases in the production of inflammatory mediators (IFN-gamma is a major pro-inflammatory cytokine), tryptophan metabolism in the kynurenine pathway starts occurring primarily outside the liver. In addition, because there is so much
IDO in the brain, much of this extrahepatic IDO metabolism occurs in the brain, often with very dire outcomes, one of the most important being serotonin depletion. As you might expect, this serotonin depletion can lead to depression and quite possibly a host of other neurologic abnormalities. Myint and Kim state:

“The tryptophan breakdown is enhanced through the activity of indoleamine 2,3-dioxygenase (IDO) enzyme, which is activated in an inflammatory state. It acts as a bridge between immune function and serotonergic abnormalities due to lack of sufficient tryptophan availability. Enhanced tryptophan degradation via the activity of IDO induced by pro-inflammatory cytokines, which in turn results in serotonin depletion, development of depression and the further imbalances in the downstream tryptophan metabolites inducing neurotoxic changes through alterations in NMDA-glutamatergic neurotransmission interaction, was proposed in the ‘neurodegeneration hypothesis of depression’, as a pathophysiological mechanism which in the end results in vulnerable glial-neuronal network.”

How does IDO-induced increases in tryptophan metabolism through the kynurenine pathway contribute to other neurologic disorders? Haroon et al point out:

“In the CNS, kynurenine can be further catabolized into the neuroactive metabolites kynurenic acid (KA) and quinolinic acid, both of which have also been found to be increased in the CSF of IFN-α-treated patients. Quinolinic acid, which is produced primarily in microglia and infiltrating macrophages, can directly bind to the N-Methyl-D-aspartate (NMDA) receptor, leading to the release of glutamate. Quinolinic acid is also associated with lipid peroxidation and oxidative stress. In combination, these activities of quinolinic acid can lead to excitotoxicity in the brain, and therefore, excessive quinolinic acid has been implicated in a number of neurodegenerative disorders, including Huntington’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, and dementia secondary to infection with HIV. Of note, increased concentrations of CSF quinolinic acid were significantly correlated with depressive symptoms in IFN-α-treated patients.”

Furthermore, if that were not enough, not only does IDO decrease serotonin and melatonin production by redirecting tryptophan metabolism away from serotonin and melatonin production, it will also directly increase metabolism of serotonin and melatonin. Myint and Kim state:

“…any inflammatory condition…might enhance the tryptophan degradation and that in turn induces low tryptophan availability for synthesis of serotonin in the brain and induces depressive behavior. Unlike TDO, the enzyme IDO is not specific only to tryptophan and degrades any compound which has an indole ring structure. Therefore, in an inflammatory condition, the IDO is activated, and serotonin is degraded not only by monoamine oxidase (MAO) into 5-hydroxyindole acetic acid (5HIAA), but also by IDO into formyl-5-hydroxykynurenine (f5OHKYM). This additional enzyme reaction further reduces the serotonin availability for optimal serotonergic neurotransmission. In addition, IDO also degrades melatonin (Acetyl-5-hydroxytryptophan to N-acetyl-N-formyl-5-methoxykynuramine (AFMK). Therefore in an inflammatory condition, melatonin level can also be reduced.”

I realize that this is very complicated neurochemistry. Therefore, I would like to highlight three key takeaway points that are important clinically:

First, with good health, there is an optimal balance between the serotonin and kynurenine branches of tryptophan metabolism. Second, for a very good reason, the production of vitamin B3/NAD, most of the tryptophan is metabolized through the kynurenine branch. In addition, it occurs mainly in the liver and is regulated by the enzyme TDO. Since the activity of this enzyme is regulated by the amount of tryptophan available, its activity is highly unlikely to reduce serotonin levels or increase production of neurotoxic compounds. Third, with ill-health, which almost universally involves upregulation of inflammation, the kynurenine branch of tryptophan metabolism is
largely transferred from TDO-mediated pathways in the liver to IDO-mediated pathways, many of which are found in the brain. In turn, with chronic inflammation, high amounts of IDO-induced neurotoxic tryptophan/kynurenine metabolites will be produced which can contribute to several neurologic health issues. Furthermore, less serotonin and melatonin will be present in the brain not only because tryptophan has been diverted away from their production but increased IDO-mediated breakdown of these neuroregulatory factors is occurring.

In part II of this series, I will finish this 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. Clinically, the research I will present makes a very strong case that, by optimizing tryptophan and kynurenine metabolism, major inroads can be made with the behavioral and cognitive signs and symptoms often seen with the many patients suffering from insulin resistant states.

Niadoxene Select™ – Moss Nutrition
Contents: 100 Vegetarian Capsules