The Kynurenine Pathway:  Modeling the Interaction between Genes and Nutrition in Schizophrenia

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Abstract  A plethora of metabolic, genetic and environmental differences have been reported for those who suffer with the mental illness known as schizophrenia. The large volume of research represents an opportunity for all those who desire to understand the basis for this disorder, but at the same time the divergent theories can appear overwhelming. What this review attempts to do is to bring together many pieces of data into a cohesive framework, focusing on two prescient observations made by a dedicated psychiatrist and researcher years ago. Abram Hoffer put forth a treatment strategy for schizophrenia based on the B3 vitamins, but also pursued another endogenous biochemical called adrenochrome, which he perceived might be etiologic for the disease. Many decades later, there is ample evidence that both theories have merit and may be functionally related through nutritional, immuno-modulatory and genetic regulation of the kynurenine pathway.

Introduction  Increases in kynurenine pathway metabolites have been an enduring finding in studies of CNS samples of schizophrenia patients over the past decade, results that are reported to be independent of medication effects (Figure 1, p.60). Activation of the pathway is not specific for schizophrenia, though many other disease entities that stimulate kynurenine synthesis can also involve psychotic features. These include bipolar disorder; pellagra; porphyria, as the suboptimal heme is restored to physiologic levels; infection-induced meningitis and encephalitis; and theoretically, steroid-induced psychosis, where the kynurenine-synthesizing enzyme, tryptophan 2,3-dioxygenase (TDO2), is likely activated via corticosteroids binding to the glucocorticoid receptor, followed by activation of the TDO2 glucocorticoid response element Elucidating a particular pattern of metabolites or unique end product specific to schizophreniform-psychosis remains a focus of much research. However, it is likely that the multifaceted pathway functions must be fully appreciated before the untoward consequences will be clearly illuminated and understood.

Kynurenine Pathway Function  The function of the most immediate consequence to survival is the generation of NAD (nicotinamide adenine dinucleotide) from tryptophan under conditions of dietary insufficiency of the vitamin B3’s (Figure 1, p.60). NAD fulfills the essential bioenergetic role of carrying reducing equivalents in the form of hydrogen atoms for many of the redox reactions necessary for life. In addition, the NAD/NADH ratio is involved in regulation of gene silencing via the PARP and sirtuin mechanisms and in that regard, may also be important in controlling the pathogenicity of some microorganisms.
Figure 1. Summary of analytical results for kynurenine pathway components, showing key points of interaction with genes of relevance to schizophrenia. The significant changes that had been identified for bipolar disorder (not shown) were limited to increased kynurenine and increased mRNA for the HM74 receptor. TDO2, HM74A and HM74 had been analyzed in previous studies for mRNA (RT-PCR) and protein (via quantitative Western blots or semi-quantitative immunohistochemistry) and several of the remaining enzymes had been analyzed for mRNA expression only (RT-PCR). The metabolites were quantified by HPLC. Enzymes are presented in boxes and denoted with their HUGO identifier. Not all steps are depicted, e.g. the signaling cascades for the receptors. Not shown is the conversion of nicotinamide to NAD.
pathway end-product nicotinamide has been shown to have anti-tubercular properties in-vivo, possibly through its actions to increase NAD levels in the non-infected tissue compartments of the host, as M. tuberculosis (MTb) is fastidious about depleting the host’s NAD and nicotinamide levels. 29-33 Of the two enzymes that activate the pathway, tryptophan 2,3-dioxygenase (TDO2) and indoleamine dioxygenase (IDO), it has been shown that TDO2 exhibits the characteristics compatible with regulation in response to NAD levels. TDO2 is responsive to feedback regulation by NAD and its congeners and it has a relatively high turnover capacity as compared to IDO, a characteristic essential for rapid regeneration of NAD. 34-38

Beyond regulating NAD, the pathway is important to the immune response via control of tryptophan levels and through the generation of immune modulators and endogenous antibiotics. Most of the immune-responsive regulation of this pathway likely occurs through IDO. IDO has a much lower Km for tryptophan (3–20 µM), than does TDO2 (100–200 µM), and thus, is capable of depleting tryptophan to very low levels. 39-42 Adequate tryptophan is important to the survival of rapidly replicating organisms, and it has been shown that replenishing tryptophan will reverse the antibiotic effect of this pathway towards some organisms. 43 Preventing a build-up of tryptophan is also important in preventing over-activation of T-cells and an intermediate derived from tryptophan metabolism through the pathway, 3-hydroxyanthranilic acid, exerts an immunomodulatory effect on T-cell function. 44 In addition, the pathway produces the endogenous antibiotic, cinnabarinic acid (Figure 2, p.62), in both mammals and lower organisms. 45,46 Cinnabarinic acid is active against bacteria, and for that purpose, it is produced by fungi in their natural environment. 47 The two enzymes that catalyze the formation of cinnabarinic acid are laccase and ceruloplasmin. 48

An additional function of the kynurenine pathway is the production of melanin-like pigments, which may represent yet another aspect of the innate immune response. 49 In insects, conversion of tryptophan to 3-hydroxykynurenine is the main route by which the eye pigments, the xanthommatins are formed. 50 In humans, xanthommatin formation is thought to be involved in the coloration of cataracts, and an etiologic role for IDO in cataract formation is an active area of research. 51-53 Melanin formation also occurs from an intermediate of the pathway, 3-hydroxy-kynurenine, but the regulation of that synthesis is poorly understood. 54 Melanins are increasingly recognized as essential in a wide variety of roles, ranging from protection against UV light, to the less well-recognized control of redox potential, protection against ionizing radiation, and sequestration of toxins. 55-59

However, many of the precursors to melanin are cytotoxic and at least two intermediates in melanin synthesis are reported to be psychotomimetic: adrenochrome and its congener, adrenolutin. 56-63 The path to adrenochrome formation commences with the methylation of norepinephrine in the brain by phenylethanolamine N-methyltransferase (PNMT) forming the catecholamine epinephrine, which then can be oxidized by one of two pathways: 1) oxidation by monoamine oxidase (MAO) to form 3,4-dihydroxy-mandelic acid, or first methylated by catechol-O-methyltransferase (COMT) to form metanephrine and then oxidized by MAO to form vanilmandelic acid (4-hydroxy-3-0-methoxy-mandelic aldehyde) or 2) oxidation by copper ions or copper-ion containing enzymes to form adrenochrome. 64-67 Adrenochrome can then form melanin, a process that is enhanced by the presence of the antipsychotic chlorpromazine. 68-72 However, the vast majority of epinephrine is metabolized and excreted in the urine as vanilmandelic acid and metanephrine. 71 Of note, the urine of children with psychosis, but not normals or children with other disorders, has been reported to be positive for N-methylmetanephrine, a finding suggestive of a general buildup of epinephrine metabolites of one form or another in psychosis. 72
Figure 2. 3-hydroxyanthranilic acid inhibits the formation of fully polymerized melanin \textit{in vitro}, as derived from Soddu et al., (2004). Shown is the classic tyrosinase-catalyzed reaction from dihydroxyphenylalanine (DOPA) as well as the reactions from the catecholamines, epinephrine and dopamine, as reviewed by Graham (1978). 3-hydroxyanthranilic acid and 3-hydroxykynurenine promote the formation of soluble pigmented material, rather than fully polymerized melanin. In the author's summary, they conclude that the inhibition of melanin formation by 3-hydroxykynurenine and 3-hydroxyanthranilic acid did not occur by direct inhibition of the enzyme, but rather occurred due to interaction between these kynurenine products and chemical intermediates of the melanin formation pathway. Note the formation of adrenochrome, a stable oxidation product of epinephrine. Depicted by the large block arrow are agents (tyrosinase, ceruloplasmin, phenothiazines) that will, to a greater or lesser extent, “chaperone” the reactions towards the formation of fully polymerized melanin. Note that there is overlap in the substrates affinities of tyrosinase and ceruloplasmin. Tyrosinase will catalyze the oxidation of DOPA, dopamine and epinephrine to form melanin. Ceruloplasmin catalyzes the oxidation of dopamine and epinephrine, facilitating the formation of melanin from epinephrine rather than adrenochrome. Phenothiazines can facilitate the formation of melanin from the oxidized reaction products of DOPA, dopamine and epinephrine in-vivo and in-vitro. Divalent copper ion can non-enzymatically catalyze all three branches of the oxidation pathway without the presence of enzyme. Not shown in the figure is 3-hydroxykynurenine, which would interact in a similar mode to 3-hydroxyanthranilic acid.
Through analyses of the kynurenic acid pathway metabolites in postmortem human brain samples, 3-hydroxyanthranilic acid has been identified as the last in the series to show increased concentration in individuals with schizophrenia. The second metabolite in the series, quinolinate (analyzed by the author, unpublished data) was found to be virtually identical in concentration in case and control samples using ion-pair reversed chromatography and methods published elsewhere. Of relevance to the potential for forming pschotomimetics, 3-hydroxyanthranilic acid and 3-hydroxykynurenine are reported to inhibit the formation of the fully polymerized, melanin end product derived from the oxidation of DOPA and/or catecholamines, leading instead to the accumulation of soluble pigmented intermediates (Figure 2). Whether or not adrenochrome might be one of the accumulated products is not yet known. This finding may relate to earlier reports of functional antagonism between activation of the kynurenine pathway and melanin generation by the enzyme tyrosinase.

**Nutrition and Regulation of the Kynurenine Pathway**

**Niacin and Nicotinamide**

First and foremost, the regulation of the pathway by niacin and its congeners is clearly evident in victims of pellagra, the vitamin B1 deficiency that leads to upregulation of the kynurenine pathway and a host of symptoms, including psychosis and eventual death if left untreated. Niacin and nicotinamide are highly effective in reversing pellagra due to negative feedback regulation of TDO2 by NAD, nicotinamide and to a lesser extent, niacin itself. Conversion of niacin to NAD would indirectly lead to more feedback regulation of TDO2 than niacin (Figure 3). Niacin is reported to be more effective than nicotinamide in restoring NAD levels, though its uptake into brain tissue, and therefore, effect on brain NAD levels, occurs at a rate approximately 1/10th that of nicotinamide. Administration of nicotinamide has been shown to restore tryptophan levels to near-normal in patients suffering from tryptophan depletion as a result of kynurenine pathway activation during AIDS or pellagra. In contrast, there is little effect on tryptophan and its metabolism to kynurenine if nicotinamide is administered under conditions when the kynurenine pathway is not activated.

Niacin may also have an effect on the kynurenine pathway via either of two nicotinamide receptors (HM74A, and HM74) as discussed below, under the section entitled: Alterations in kynurenine pathway genes: TDO2 and the niacin receptor genes.

Analyses of niacin levels in tissue and blood samples have been attempted by this author, but the concentrations in human tissue and blood samples were below the detection limit (approximately 10 µM) using methods previously reported. Nicotinamide was easily detected and was found to trend lower in postmortem anterior cingulate brain samples from schizophrenia patients, though the difference was not significant. Table 1, (p.65) shows the serum versus whole blood values for nicotinamide in a series of three subjects, illustrating the remarkable absence of nicotinamide in the serum (below the detection level of the method) but the consistent whole blood values between the subjects. Thus, reports of “concentration-independent” transport of nicotinamide from the blood to the brain should be viewed with caution, since plasma values for nicotinamide were used as the benchmark, rather than whole blood.

The work of Abram Hoffer has encompassed orthomolecular approaches to treating schizophrenia, with a focus on the beneficial effects of niacin and nicotinamide. Several groups followed up with clinical studies on this approach, with mixed success. Of note, the most successful studies employed niacin alone (Table 2), rather than a vitamin B3 formulation of unspecified composition. Although both niacin and nicotinamide are considered vitamin B3, they are quite different in terms of their other biochemical functions and in mammals, cannot be readily interconverted as mammals lack the necessary deamidase, Pnc1. Importantly, nicotinamide: a) is not active at either of the
niacin receptors; b) inhibits gene silencing, unlike niacin, which stimulates gene silencing; and c) if anything, is anti-diabetogenic, unlike niacin.

Tryptophan

Tryptophan loading in the diet will activate the kynurenine pathway (Table 3a, p.66), serving to divert excess tryptophan away from serotonin synthesis in the brain when levels become too high (Figure 1). Approximately 40% of brain kynurenine is derived from tryptophan, and at tryptophan loading doses above 25 mg/kg, sero-
Table 1. Large differences between whole blood and sera analyses for kynurenine pathway metabolites in a series of three subjects, demonstrating high inter-subject variability in sera and less variability in whole blood, using methods published elsewhere.7

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tryptophan, µM</th>
<th>Kynurenine, µM</th>
<th>Nicotinamide, µM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>55.5</td>
<td>0.60</td>
<td>67.8</td>
</tr>
<tr>
<td>B</td>
<td>27.0</td>
<td>0.53</td>
<td>74.4</td>
</tr>
<tr>
<td>C</td>
<td>20.7</td>
<td>0.49</td>
<td>69.4</td>
</tr>
<tr>
<td>Serum</td>
<td>13.0</td>
<td>0.33</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>0.15</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>0.10</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Table 2. Number of studies showing a positive effect, no effect and a negative effect, based on type of vitamin B₃ formulation that was utilized

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Positive effect</th>
<th>No effect</th>
<th>Negative effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>niacin alone</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>vitamin B₃</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>niacin and nicotinamide composition unspecified</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>nicotinamide alone</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Tryptophan brain levels can become paradoxically depleted, as proportionally more serotonin is degraded to hydroxyindoles and more tryptophan is directed towards kynurenine synthesis.92,93

In work carried out during the middle of the last century, Benassi determined that tryptophan loading in schizophrenia patients led to accumulation of kynurenine metabolites in the urine of both controls and patients with schizophrenia, though the accumulation was significantly higher in the patients (Table 3b p.66).90 Gilka (1978) suggested that the greater accumulation of kynurenine metabolites in schizophrenia was likely due to a block at the level of 3-hydroxyanthranilate oxidase (HAAO) shown to be of significantly lower activity in blood samples of schizophrenia patients, and Hoffer (1979) concurred.94-96 Their perspective is certainly supported by the finding that 3-hydroxyanthranilic acid is the last metabolite in the pathway sequence shown to be elevated in concentration in postmortem anterior cingulate samples of individuals with schizophrenia, as described above.7

The correspondence between endogenous tryptophan levels and the kynurenine pathway activation in patients versus controls is not straightforward. Domino and Krause (1974), found a significantly lower fasting tryptophan level in the plasma of unmedicated acute schizophrenic subjects, but slightly higher fasting plasma tryptophan in medicated chronic schizophrenics.97 More recent studies have shown lower tryptophan serum levels in first episode, drug naive patients and low serum tryptophan in both the medicated and unmedicated state.98,99 Barry et al. (2009) demonstrated significantly greater peripheral tryptophan degradation in medicated schizophrenia patients, as well
as a non-significant trend towards lower tryptophan levels in the sera. A caveat for the preceding studies, however, is that sera or plasma measures were used, rather than whole blood analyses. We have found that, similar to the situation with nicotinamide, whole blood contains markedly more tryptophan than sera and the inter-patient values are more consistent in whole blood (Table 1). The mean value for sera that we identified (5.4 µM) is very close to the mean values shown by Badawy et al. (2005) for a series of samples derived from chronic fatigue patients.

In that study, Table 3a. Fold difference in urine, between basal levels within each group and levels following supplementation with tryptophan

<table>
<thead>
<tr>
<th></th>
<th>children 100 mg/kg suppl(\text{a})</th>
<th>adult males 100 mg/kg suppl(\text{b})</th>
<th>adult pellagrins no B(\text{6}) approx 30 mg/kg suppl(\text{b})</th>
<th>adult pellagrins +B(\text{6}) approx 30 mg/kg suppl(\text{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kynurenine</td>
<td>17.5</td>
<td>29.4</td>
<td>27.8</td>
<td>4.5</td>
</tr>
<tr>
<td>3-OH-kynurenine</td>
<td>1.7</td>
<td>6.0</td>
<td>43.7</td>
<td>9.8</td>
</tr>
<tr>
<td>3-OH-anthranilic acid</td>
<td>3.1</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthranilic acid</td>
<td>5.9</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kynurenic acid</td>
<td>12.0</td>
<td>14.4</td>
<td>18.1</td>
<td>17.2</td>
</tr>
<tr>
<td>Xanthurenic acid</td>
<td>4.5</td>
<td>7.0</td>
<td>9.4</td>
<td>8.5</td>
</tr>
</tbody>
</table>


Table 3b. Increase (fold-difference) in mean urine kynurenine metabolites in schizophrenia patients versus controls

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Fold difference** in metabolites(\text{c}) between schizophrenia patients(\text{d}) and normals after loading with 100 mg/kg tryptophan, matched for age, weight, gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kynurenine</td>
<td>3.4*</td>
</tr>
<tr>
<td>3-OH-kynurenine</td>
<td>8.5*</td>
</tr>
<tr>
<td>3-OH-anthranilic acid</td>
<td>*** 0.9</td>
</tr>
<tr>
<td>Anthranilic acid</td>
<td>n.d.</td>
</tr>
<tr>
<td>Kynurenic acid</td>
<td>1.6*</td>
</tr>
<tr>
<td>Xanthurenic acid</td>
<td>2.3*</td>
</tr>
</tbody>
</table>

* statistically significant, p<0.005  ** as no basal values were given for either controls or patients, it is impossible to know if the controls and patients differed in basal values as well.  *** it is notable that the 3-OH-anthranilic acid did not increase above the increase seen for controls, particularly because no psychotic symptoms were observed.

\(c\). Derived from Benassi et al. (1961)\(90\)  \(d\). Although not specified by authors, patients were likely medicated.
the authors noted the “heterogeneity” of serum tryptophan concentrations, arguably a reflection of the sample source. Therefore, whole blood analyses should be performed whenever possible.

In regard to tryptophan in the brain, Issa et al. (1994) found elevated tryptophan in the CSF and Miller et al. (2008) found elevated postmortem brain tryptophan levels in patients with schizophrenia, outcomes that did not appear to be influenced by the medication status of the patients.7,102 The divergence in the direction of the patient-control difference for brain and sera is plausible, as many factors influence the uptake of amino acids into the brain. Lenard and Dunn (2005) have shown that free fatty acids can increase brain tryptophan uptake in an animal model, as can β-adrenergic agonism, cytokines and lipopolysaccharides.103–105 A higher brain concentration of tryptophan is more consistent with pathway activation by TDO2 in schizophrenia, rather than IDO, as TDO2 is not as effective in lowering tryptophan concentrations.7,16,39–42 However, with all the kynurenine metabolites measured to date, it pays to keep in mind that there is substantial overlap in the values between cases and controls and individual patients may exhibit metabolite levels reflective of different enzymatic patterns of activity.7

Despite the clear build-up of kynurenine metabolites with tryptophan loading, the effect on mental symptoms is not straightforward.90 In fact, there is no evidence that tryptophan loading alone can exacerbate schizophrenia or elicit psychosis in normal individuals.90,106,107 Studies showing psychotomimetic effects have involved concomitant methionine supplementation plus an MAO inhibitor, with results that were most probably attributable to the methionine itself.108–111

Yet the possibility that kynurenine pathway activation is not etiologic is effectively ruled out by the finding of a genetic association between schizophrenia and the genetic locus for TDO2 (see section below: Alterations in kynurenine pathway genes: TDO2 and the niacin receptor genes).112 In all likelihood, two conditions must simultaneously exist: 1) other key interacting genes must be present in the tryptophan-loaded individuals; and 2) the nutritional methylation status must be such that the generation of additional endogenous psychotomimetics is possible. For example, the biomarker of depleted methylation status, homocysteine, is commonly found to be elevated in schizophrenia.115 Thus, methylation would be expected to be a limiting factor in the generation of additional methylated products (beneficial or otherwise), and only through supplementation with methionine or folate would the methylation capacity be restored. A methylation defect has been proposed to be important to the disease process (see section below: Folic acid, methionine and cobalamin (vitamin B12) as reviewed by Smythies (1983)).114 Restoration of methylation capacity might therefore interact with one of the tryptophan metabolites to exacerbate psychosis. Furthermore, the additional requirement for an MAO inhibitor to see the effect of methionine may relate to the balance between the catecholamine/indoleamine oxidation pathways versus other metabolic fates for the biogenic amines. Blocking oxidative degradation by MAO enzymes with the MAO inhibitor would shift the balance more towards oxidation via copper-catalyzed reactions and the associated toxic intermediates such as adrenochrome (Figure 2).60,66,67,70,73,115–125 This path would then interact with the kynurenine pathway via 3-hydroxyanthranilic acid or 3-hydroxykynurenine (Figure 2).73

Although tryptophan excess has little effect on mental status, tryptophan depletion is of more consequence. In the “depression” of pellagra, a disease commonly thought of as a deficiency in niacin and nicotinamide, there remains some question as to whether low levels of available tryptophan are ultimately more important to the disease process than depletion of the vitamin B6’s. Certainly, without a tryptophan deficiency, and barring a defect in the kynurenine pathway, the symptoms of pellagra would never develop. A diet too rich in corn, blamed for the massive outbreaks of pellagra during the depression years was notable for both a relative
deficiency of tryptophan as compared to the other aromatic amino acids and a deficiency in bioavailable niacin. To release the niacin from corn, corn meal must be prepared with a liming agent. This requirement was intuited by the Native American populations who evolved with corn as a staple in their diet, but was not well understood by Western cultures.

When the concentration of tryptophan is low, the activity of IDO becomes more important for generating the precursors of NAD based on its low Km for tryptophan as discussed above. This enzyme has been reported to exhibit a somewhat different pattern of expression than TDO2, but there is substantial overlap between the two in the cell types of expression. Where the overlap occurs, Guillemin. (2007) determined that the expression of TDO2 and IDO are inversely coordinated in the same cells. Coordination of IDO expression also occurs with other enzymes of the kynurenine pathway in response to IFNG stimulation, leading to more quinolinate production relative to other products such as kynurenic acid and picolinic acid.

A chronic deficiency of tryptophan would be expected to exacerbate not only pellagra, but also to engender greater susceptibility to infectious organisms whose growth is inhibited by kynurenine pathway metabolites, but which are relatively less affected by low tryptophan levels. A lesser requirement for otherwise limiting nutrients is typically seen in slow-growing organisms, an example of which is MTb. MTb is unusual in that resistance to this organism derives primarily from innate immunity rather than acquired immunity. In this regard, the kynurenine pathway represents one component of the innate immune system. Of note, human MTb has evolved to secrete copious quantities of niacin, generated by the organism from NAD and nicotinamide, and leading to depletion of the latter two biochemicals in the host. In point of fact, niacin was detected (mean value, 15 µM) by this author in whole blood samples from two MTb infected, isoniazid-treated mice (3 and 25 mg/kg, respectively, treated for 3 weeks), but could not be detected in matched controls treated with isoniazid, using analytical methods described previously by Miller et al.,(2008). In addition, NAD was depleted by an average of 28% and nicotinamide by 22% in the infected animals as compared to the controls. The function of the excess niacin is likely the activation of the human niacin receptor (Figure 3) with concomitant negative feedback effects on kynurenine formation via the striking elevation of PGE2 seen in MTb-infected mice, acting to block the requisite activation of IDO by TNF-α (Figure 3). Defective niacin receptors would obviously be less sensitive to this adaptive strategy of MTb. Thus, a model for genetic vulnerability to schizophrenia in generations following severe MTb epidemics has been previously proposed by Miller et al. (2009) and is consistent with the niacin-receptor gene mutation associated with schizophrenia, as discussed below. Inadequate protein nutrition and tryptophan nutrition specifically, may have played an important role in fostering those MTb epidemics by diminishing kynurenine pathway function.

Vitamin B6

Much of the work on vitamin B6 and the kynurenine pathway was conducted by Dr. Hellen Linkswiler at the University of Wisconsin, Madison, during the 1960’s. Two of the pathway enzymes require vitamin B6, kynurenase and kynurenine aminotransferase, and of the two, kynurenase is more sensitive to a vitamin B6 deficiency. Thus, vitamin B6 is poised to facilitate flux through the pathway and its deficiency to impede flux, leading to the accumulation of kynurenine and 3-hydroxy-kynurenine under conditions of tryptophan loading. However, in the absence of tryptophan loading or a high protein diet, vitamin B6 deficiency by itself does not consistently cause an abnormal buildup of kynurenine metabolites in the urine. With tryptophan loading during B6 deficiency, kynurenic acid has been shown to increase, which can be explained by the dependence of kynurenine-amino-transferase (KAT) on
vitamin B6 (Figure 3). Xanthurenic acid, another product of KAT derived from 3-hydroxykynurenine (Figure 3), increased more markedly with tryptophan loading, raising the possibility that one isoform of KAT may be less sensitive to B6 than another.

In pellagral victims given vitamin B6 as compared to those not given the supplement, the buildup of xanthurenic acid in urine samples was found to be reduced along with levels of kynurenine and 3-hydroxykynurenine but quinolinic acid and N-methylnicotinamide were increased.

There are no reports of vitamin B6 deficiencies being associated with psychosis, but the absence of such reports is not particularly illustrative since tryptophan loading would be required to achieve differential buildup of specific pathway metabolites. Nevertheless, in experiments involving B6 depletion and tryptophan loading, psychosis has not been mentioned as a side effect.

**Omega-3 Fatty Acids**

A positive role for omega-3 fatty acids in mitigating the symptoms of schizophrenia has been suggested by some studies, but not confirmed by others. The interaction of omega-3’s with the kynurenine pathway is not fully understood, but would be likely to occur at two crucial points (Figure 3), the inhibition of phosphatidylcholine synthesis (through competitive inhibition with omega-6 fatty acids) and through a negative impact on cyclooxygenase (COX). The net result would be a decrease in prostaglandin D2 and E2 synthesis and therefore, greater lipolysis (Figure 3). In this regard, omega-3’s counteract the effect of niacin to depress lipolysis. Niacin stimulates arachidonic acid release via PLA2 and also in some macrophage cell types in a PLA2-independent manner. The receptors for PGE2 and niacin (see below) negatively regulate lipolysis in fat cells via elevating cAMP.

The inhibitory effect of omega-3-fatty acids on omega-6-fatty acid incorporation into membrane phospholipids is one of competition but the negative effect of omega 3’s on COX activity is thought to occur via regulation of gene expression.

Thus, omega 3 fatty acids are poised to diminish upregulation of the kynurenine pathway via inhibition of PGE2 formation, thereby preventing PGE2 induction of IDO mRNA synthesis. An adequate dose of omega 3’s would be crucial, as the effect of PGE2 itself on IDO activation is bell-shaped, i.e. at high levels PGE2 prevents the requisite activation of IDO by TNF-α; at low levels, no PGE2-induction of IDO mRNA transcription occurs; but at moderate levels PGE2 stimulates IDO mRNA transcription and does not block TNF-α activation of the IDO enzyme.

**Copper**

Copper is a mineral that is an essential cofactor for several classes of oxidative enzymes, and when present in excess, is a cause of oxidative stress. The range of concentrations that promote health is quite narrow, in as much as the recommended adequate daily intake for an adult is 1.5 mg to 3 mg and only 4 times that amount can be safely consumed. Total copper (free plus bound) is equally distributed between the cellular and sera components of blood, each approximately 16 µM, whereas the normal liver is reported to contain 96 µM and the CSF, approximately 80 µM.

The copper hypothesis of schizophrenia was once taken quite seriously by researchers around the world, as reviewed by Bowman and Lewis (1982), based on the consistent findings of elevated copper levels in blood and tissue samples of patients. Another basis for this theory was the observation that Wilson’s disease, which involves an accumulation of copper, is associated with psychiatric manifestations. Reports on the prevalence of psychotic psychiatric disease in Wilson’s disease range from 2% as reported by Denning and Berrios (1989) to 11% as reported by Huang and Chu (1992), to 18% for bipolar disorder as reported by Shanmugiah et al. (2008), although greater than 50% are diagnosed with some sort of psychopathology. Occasionally, psychosis is the first manifestation of disease.
The copper accumulation is now known to result from a defect in a copper transport gene (ATP7B) which often leads substantial reduction in the levels of ceruloplasmin, but not always. Ceruloplasmin is a strong chelator of copper, utilizing the metal for a variety of redox reactions. This enzyme is thought to contain >95% of the copper present in vertebrate sera, incorporating at least 6 moles of divalent copper per mole of enzyme of which two are in “labile” sites, i.e. more likely to be unoccupied. “Prosthetic” copper held by ceruloplasmin is that incorporated during the assembly of the protein which cannot be removed by affinity chromatography, and is likely integral to the redox reactions in which ceruloplasmin participates. Additional “exogenous” copper binding sites exist in ceruloplasmin from which copper can be removed by affinity chromatography, which together bind copper with higher affinity than similar sites on albumin. The overall K$_{0.5}$ of these exogenous sites is likely on the order of 1.35 µM. Of note, unoccupied binding sites in ceruloplasmin may relate to why ceruloplasmin administration to schizophrenia patients was found to ameliorate symptoms, possibly through chelation of copper at the exogenous sites. An additional benefit of ceruloplasmin may be its involvement in the oxidation of epinephrine, where it promotes the formation of melanin rather than adrenochrome (Figure 2). Of note, data from studies by de Mol (1985) can be used to illustrate that the more effective antipsychotics (e.g. fluphenazine) result in lesser oxidation of catecholamines in the presence of ceruloplasmin (Figure 4, p.71), again suggestive of the potential importance of redox control in psychosis, but a view at odds with the dopamine-receptor hypothesis of schizophrenia. Importantly, the interaction of chlorpromazine with adrenochrome was studied by Galzigna (1972) who demonstrated that chlorpromazine facilitated the formation of melanin pigment from adrenochrome. The relevance of this finding to the chlorpromazine-induced hyperpigmentation seen in patients was recognized and discussed at the time. This study clearly set the stage for the concept that melanin formation might be a mechanism for removal of toxic and potentially psychotomimetic melanin precursors generated by the oxidation of dopamine and epinephrine (Figure 2).

Folic Acid, Methionine and Cobalamin (Vitamin B$_{12}$)

Folic acid, methionine and cobalamin are all key components for the generation of s-adenosyl-methionine, the methyl donor in most methylation reactions in mammals, as reviewed by Ragsdale (2008). Methylation can be regarded as tangentially relevant to the kynurenine pathway, through the methylation of niacin by COMT, the methylation of nicotineamide–N-methyltransferase (NNMT) and the methylation of a precursor of melanin, i.e. of norepinephrine to form epinephrine which would interact with the pathway as depicted in Figures 1 and 2.

Cobalamin deficiency has long been associated with psychosis, often as a present-
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Deficiencies not apparent in the serum may nevertheless result in mental symptoms that respond to treatment with this vitamin. A decreased methylation status by itself is an unlikely cause of psychosis, because folate deficiencies do not elicit psychotic symptoms. In point of fact, cobalamin-deficiency psychosis can be present when folic acid is at normal levels and in that context, supplementation with folic acid can either precipitate a psychosis or further exacerbate the symptoms. Of potential relevance to this observation, when cobalamin is low, methyl transfer from methyltetrahydrofolate is impaired (Figure 5, p.72) leading to the buildup of both methyltetrahydrofolate and homocysteine. Folate supplementation will only increase the buildup of methyltetrahydrofolate (the “methylfolate trap” hypothesis). The “methylfolate trap” pattern of folate metabolites has been documented in humans. Allen (1993) has reviewed the complex inconsistencies of models that attempt to reconcile the divergent themes of cobalamin-induced psychosis, pointing out that elevations in malonic acid and homocysteine may be consistent biomarkers for a

Figure 4. Degree of dopamine oxidation by ceruloplasmin in the presence of various antipsychotics, derived from de Mol (1985). The most effective antipsychotics (e.g. fluphenazine) result in the least dopamine oxidation. The efficacy data for the antipsychotics was derived from Seeman (1987), where the dose required for efficacy was plotted on a log scale. When analyzed in that manner, and when the apparent outlier (chlorpromazine) is excluded from the analysis, the correlation between dose required for efficacy and the dopamine oxidation effect is $r = 0.99$, $p = 0.008$. Only the drugs reported by both Seeman (1987) and de Mol (1985) were analyzed.
cobalamin deficiency but fail to distinguish cobalamin-deficient patients who have psychosis from those that do not. An alternative explanation for the psychotic side effects relates to toxic pigment formation. Cobalamin deficiency often leads to a condition of cutaneous hypermelanogenesis by as yet unknown mechanisms. That the increased pigment is melanin has been confirmed microscopically. There are two theories presented by others as to the mechanism of the increased pigmentation, reviewed by Haight and Norman (2008): 1) A cobalamin deficiency decreases the level of the reduced form of glutathione, GSH. Because GSH inhibits tyrosinase, a lack of GSH increases tyrosinase activity and melanin production; or 2) A deficiency in cobalamin leads to a lack of regeneration of tetrahydrofolate (Figure 5), accumulation of methyltetrahy-
drofolate as reviewed by Scott (1999) and as a consequence, increased tetrahydrobiopterin, a limiting cofactor in catecholamine biosynthesis.²⁰⁰⁻²⁰³

In the latter scenario, the resulting increase in catecholamines would translate into increased degradation of the catecholamines via methylation, oxidation and/or melanin production. However, the latter pathway should be counterbalanced by the high tetrahydrobiopterin levels, which inhibit tyrosinase and potentially cause increased catecholamine oxidation via copper-catalyzed generation of o-quinones (Figure 5).²⁰⁴ Theoretically, the result would be accumulation of oxidized melanin precursors such as the psychotomimetic compound adrenochrome (Figures 2 and 5).

Of note, psychosis has not been reported in any case of cobalamin deficiency where increased deposition of polymerized melanin effectively occurs. Thus, the prediction would be that in those whose tetrahydrobiopterin level is too high (Figure 5), adrenochrome would be produced from the increased catecholamine degradation instead of melanin.

**Gene-gene Interactions Relevant to Kynurenine Pathway Function in Schizophrenia**

**Relevance of Alterations in Kynurenine Pathway Genes: TDO2 and the Niacin Receptor Genes**

Much work on the cause of kynurenine pathway activation in schizophrenia and bipolar disorder revealed gene expression changes in the enzyme TDO2 and in the niacin receptors, HM74A and HM74.⁶,⁷,¹⁶,²⁰⁷ TDO2 expression was found to be increased and the high affinity niacin receptor protein expression decreased in postmortem brain samples of patients with schizophrenia.⁶,¹⁶,²⁰⁷ Activation of HM74A by niacin leads to increased PGD2 and PGE2 production, of which PGD2 is thought to be primarily responsible for eliciting the flush response.²⁰⁸,²⁰⁹ High PGE2 is responsible for blocking the synthesis of TNF-α, a cytokine essential for the full activation of IDO (Figure 3).¹³⁶,¹³⁷ In individuals with a defective HM74A receptor, initiation of this cascade would be prevented, leading to the blunting of the flush response observed in many schizophrenia patients but allowing full activation of IDO enzyme activity (Figure 3).²⁰⁷ Our studies of IDO in schizophrenia were limited to mRNA expression and finding no difference, we failed to proceed in studies of the protein or enzyme activity.¹⁶ Thus, kynurenine pathway activation in different individuals with schizophrenia could theoretically be initiated by either increased TDO2 synthesis or undue activation of the IDO enzyme stemming from the niacin receptor defect.

Overcoming the defect in the niacin receptor may be possible by administering large amounts of supplemental niacin, as treatment of schizophrenia patients with niacin has been shown to be highly effective in the work of Abram Hoffer (1957,1962), particularly in the early, acute phase of the illness.¹,⁸¹ As discussed above, the majority of studies that successfully replicated Abram Hoffer’s work utilized niacin alone, rather than nicotinamide or a combination of the two (Table 2).⁸² This would imply some advantage specific to niacin itself, rather than an indirect effect through the generation of NAD which occurs from either niacin or nicotinamide. Since nicotinamide does not activate either the high affinity or low affinity niacin receptors, the receptors would be one route by which specificity for niacin would be conferred.

However, there is some debate about whether or not niacin itself is the endogenous ligand for these receptors, because the niacin concentration required for activation are cited as being quite high.²¹⁰,²¹¹ Other reports demonstrate that niacin concentrations required for receptor activation vary according to the cell system studied. Thus, while Tunaru et al. (2003) demonstrated the EC50 for HM74A to be approximately 5 µM in CHO-K1 cells; Wise (2003) reported the EC50 to be 0.13 µM to 0.25 µM for in Xenopus oocytes and HEK293T cells, respectively; and Walters (2009) reported the EC50 to be 0.018 µM in their cell system of HEK-293 cells.⁸⁴,²¹⁰-²¹²
Consequently, the reported range in EC50 is large, from 0.018 µM to 5 µM niacin. The range of plasma concentrations of niacin reported using current analytical methodology are reported by Saika et al. (1999) to be 0.08 µM, but ranging to 0.4 µM, as reviewed by Tunaru et al. (2003) and hence, overlapping with the lower range of the reported EC50 values.210,211 Furthermore, whole blood and tissue levels of niacin have been found to be roughly 100-fold higher than that seen in plasma or the serum using microbiological assays and are reported to be as high as 4 µM in brain tissue using quantitative mass spectrometry methods.214-216 While keeping in mind the potential inaccuracy of the older microbiological methods, the trends in the results again point to the importance of measuring whole blood concentrations, particularly since cellular uptake mechanisms for niacin exist that are independent of HM74A.214,215,217,218 For other reasons, the intracellular levels may well be more pertinent to the high affinity niacin receptor, as immunohistochemistry suggests that the receptor may localize at the nuclear envelope (postmortem anterior cingulate cortex brain tissue, unpublished data from our laboratory) and preliminary confocal microscopy is also suggestive of that localization (Dr. Martin Savard and Dr. Fernand Gobeil, human brain microvascular endothelial cells, personal communication), as seen with other members of the G-protein-coupled receptor family.219

After dosing with pharmacologic amounts of niacin capable of eliciting the flush response, niacin can be detected in the plasma at levels as high as 60 µM or with fast release formulations, 250 µM.220,221 What blood levels might be reached postprandially has not been studied, yet it is clear that flushing is not commonly experienced after eating niacin-rich foods. However, activation of this receptor is not always coupled to prostaglandin synthesis, as demonstrated by Walters and others (2009).212 By using the “biased” agonist MK-0354, they determined that this agonist was able to repress lipolysis without inducing the conformation necessary to initiate the involvement of β-arrestin, required for the prostaglandin cascade. Thus, as found in some cell systems for niacin itself, activation of the HM74A receptor by this “biased” ligand can directly depress lipolysis independent of the depression of lipolysis by prostaglandin E2.153,154

Some have proposed that β-hydroxybutyrate (BHB) may be the endogenous ligand for HM74A. The EC50 of BHB for HM74A is on the order of 800 µM, which is above the normal physiologic range but well within the levels reached during ketosis.222 Given the crucial role of HM74A in controlling lipolysis, this scenario would be consistent with feedback inhibition of ketone generation from ongoing lipolysis when ketosis becomes too extreme. In all likelihood, both niacin and BHB are endogenous ligands for this receptor, a receptor for which the full range of functions have yet to be identified.

Whether kynurenine pathway activation is etiologic for schizophrenia, or merely a nonspecific biomarker, was addressed by demonstrating that genetic polymorphisms in kynurenine pathway components are significantly associated with this disorder (TDO2 and the low affinity niacin receptor, HM74).112 The polymorphism selected for study in HM74A itself was not in Hardy Weinberg equilibrium, rendering any assessment of its association inaccurate. Thus, the association of schizophrenia with the closely linked HM74 cannot at this time be distinguished from an association with the HM74A gene. Of note, the risk allele identified for HM74 was previously identified as being significantly associated with bipolar disorder, and an association with the patient group that included bipolar disorder patients was also identified by this author.112,223 This outcome is inconsistent with studies showing no difference between bipolar patients and controls in the flush response and raises the possibility that defects in receptor function can exist that are unrelated to flush but are nevertheless relevant to mental function.

Possible functional effects of the polymorphisms associated with disease was a question we addressed by comparing the relationship between the risk alleles and
mRNA expression in normal control, post-mortal anterior cingulate brain tissue samples (expression data derived from previous work). The polymorphism (rs2271537) in TDO2 is intronic and that in HM74 (rs2454727) lies within the exon, resulting in a nonsynonymous change (an isoleucine replacing a methionine). Both polymorphisms were found to increase expression, 1.80-fold, p = 0.077 and 2.23-fold, p = 0.002, respectively. The direction of this difference is consistent with the higher frequency of the risk allele in cases and the expression differences seen between cases and controls.

Interaction between TDO2, the niacin receptor gene and other genes of risk were found to augment the odds of disease. Thus, HM74 was found to interact with MCHR1 and MCHR2, increasing the risk (odds ratio) from 1.5-fold to 1.7 fold. These two genes, or nearby chromosomal markers, have been shown to be associated with schizophrenia in other studies and due to their melanotropin function, are relevant to the pigment production by kynurenine pathway activation. MCHR1 specifically, is involved in the sequestration of melanin pigment. An interaction of the gene TDO2 was observed with MCHR2 and with another melanotropin receptor gene, MC5R, which together augmented the odds ratio for TDO2 from 1.5-fold to 4.84-fold. There remains ample opportunity to test interaction with other schizophrenia or bipolar-associated genes that bear some relationship to the kynurenine pathway (Figure 1), and some of these genes are discussed below.

Other Genes of Interest that Interact with the Kynurenine Pathway

Catechol-O-methyltransferase (COMT), for example, has shown a consistent association with schizophrenia, found to confer a modest degree of risk (odds ratio = 1.13) across several studies included in a meta-analysis. COMT is a methylator of niacin, generating methylnicotinate. Methylnicotinate is the formulation used to generate skin flush in epidermal tests, but whether it has activity at the niacin receptor, without first generating niacin, is not clear. Of note, it was the methyl-accepting nature of niacin that originally led Abram Hoffer to postulate that niacin might draw methyl groups away from catecholamine generation (personal communication) and therefore be beneficial for schizophrenia. This scenario still has merit, although a beneficial effect of niacin via kynurenine pathway regulation is also very likely.

Likewise, dysbindin (DTNBP1) has evidenced association with schizophrenia in several studies, conferring a slightly higher risk than COMT (odds ratio = 1.23) in the meta-analysis conducted by Allen and others (2008). DTNBP1 may interact with genes causing kynurenine pathway activation by affecting the sequestration of the pigment it produces (Figure 1), as a mutation in DTNBP1 causes leaching of pigment from vesicles.

The gene nicotinic alpha-7 cholinergic receptor (CHRNA7) has been extensively studied for association with schizophrenia, and is implicated both in terms of function and genetic association. Linkage and association analysis has been positive for markers in or close to the nicotinic α-7 receptor (CHRNA7) in schizophrenia with calculated odds ratio values of 2.1 to 2.3 for two association studies of cohorts including Caucasians and African Americans. Its interaction with the kynurenine pathway would be expected to occur at the level of kynurenic acid, an antagonist of CHRNA7. Antagonism of this receptor would be expected to worsen the symptoms of schizophrenia, based on functional studies in humans and studies in animal models.

The interferon gamma receptor (IFN-GR1) may interact with IFNγ at the promoter for IDO to affect IDO expression. Such interaction (recruitment) has been shown for IFNγ-responsive promoter elements. This gene has not been studied for association with schizophrenia, but lies in a general chromosomal region (6q23.3) that has been associated with this disease.
Tryptophan hydroxylase-1 (TPH1) has been associated with schizophrenia, conferring a modest degree of risk, an odds ratio of 1.31, reviewed by Allen (2008). Through its function to catalyze the first step towards serotonin synthesis, it is certainly an enzyme relevant to mental status. The overall expression of TPH1 was originally not thought to be as high in the brain as tryptophan hydroxylase-2 (TPH2), but more recent research shows significant region-specific expression of both enzymes. Theoretically, the ability of TPH1 to maintain serotonin synthesis in the face of depletion of tryptophan by the kynurenine pathway would be a key point of interaction.

Summary and Conclusions

Very many of the divergent theories concerning the pathogenesis of schizophrenia can be accommodated by the model as originally put forth by Abram Hoffer and as expanded upon above:

- The adrenochrome hypothesis of schizophrenia
- The niacin hypothesis of schizophrenia
- The kynurenine-pathway hypothesis of schizophrenia
- The genetic hypothesis of schizophrenia
- The copper hypothesis of schizophrenia
- The methylation hypothesis of schizophrenia
- The immune-dysregulation hypothesis of schizophrenia
- The lipid-imbalance hypothesis of schizophrenia
- The oxidative stress hypothesis of schizophrenia

The most salient point to emerge from this review is that activation of the kynurenine pathway would be expected to increase the formation of the psychotomimetic compound adrenochrome. The practical implications are that supplementation strategies involving niacin or cobalamin are clearly beneficial, but alterations in tryptophan loading in the diet seem to have little effect on psychotic symptoms. All determinations of nutrient status should be conducted on whole blood rather than serum. Copper metabolism may also be a primary defect in some patients and should be regarded as part of the larger picture of redox imbalance, as its role is that of a strong oxidant. In that regard, improving the redox status of patients through vitamin C supplementation would certainly seem wise, while strategies to deplete copper (if high) should be undertaken with care, as the healthy range for copper is quite narrow. Although vitamin B₆ plays an important role in aspects of kynurenine pathway function, there is little evidence that a B₆ deficiency is involved in generating psychotic symptoms. Supplementation with high levels of omega-3 fatty acids should be beneficial through decreasing the activation of IDO, though the clinical trial outcomes have yielded mixed success. Most clinical trials of nutrients have occurred in patients medicated with antipsychotic drugs, and the confounding effect of those powerful drugs must be taken into account.

As concluded by L. John Hoffer (2008), there is ample reason to pursue nutritional therapies in schizophrenia, ideally during the acute early-onset phase of the illness when CNS alterations underlying disease progression are not yet pronounced in nature. For some, neuroleptic drugs may be the only option, but in contrast to nutritional therapies, neuroleptics have potent side effects that prohibit a normal level of function. They create neurochemical imbalances that make withdrawal extremely difficult to achieve, as exacerbation of psychosis is virtually inevitable during the withdrawal period. Consequently, a prescription for these drugs is often a prescription for life. In the pre-neuroleptic era, it was recognized that approximately one third of those with a psychotic break would
get better over time, but that group has little hope of a normal life in today’s world of modern psychopharmacology.

Acknowledgements
I am deeply indebted to Abram Hoffer, for his visionary approach, mentorship and courageous choice of career path.

Competing Interests
The author declares that she has no competing interests.

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