Kynurenine metabolites of tryptophan:
Implications for neurologic diseases

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Article abstract—Over the past 2 decades, a number of studies have demonstrated that amino acids act as precursors for the biosynthesis of a variety of neuroactive compounds, including catecholamines and indoleamines. For example, the aromatic amino acid L-tryptophan is a precursor for serotonin biosynthesis. Based on this observed precursor relationship, dietary tryptophan supplementation is used to treat a number of neurologic disorders attributed to alterations in serotoninergic neurotransmission. Recent studies have revealed that, in addition to serotonin, a number of neuroactive compounds, the kynurenines, are metabolities of tryptophan. Of these, perhaps the most important is quinolinic acid, a neurotoxin that acts at the *N*-methyl-D-aspartate (NMDA) receptor and whose precursor responsiveness to tryptophan far exceeds that of serotonin. In the central nervous system, kynurenines, and in particular quinolinic acid, may modulate excitatory amino acid transmission, and may act as neurotoxic agents implicated in the pathogenesis of several neurologic diseases.

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Tryptophan and brain serotonin. The precursor relationship of plasma and brain tryptophan to serotonin[1,2] has led to therapeutic interventions based on oral tryptophan supplementation in several neuropsychiatric and related disorders. Included among these are depression, insomnia, aggression, obesity, and hypertension.[3-9] As a result of these speculations, self-administration of tryptophan bought at health food and other stores is now common.

Tryptophan and brain kynurenines. Although tryptophan is the precursor for serotonin biosynthesis, it is now known that its metabolism in brain is more complex. A number of studies have demonstrated that increased plasma (and therefore, brain) levels of tryptophan not only augment brain levels of serotonin, but also the biosynthesis of the kynurenines.[10-16] Of the kynurenines, quinolinic acid may be the most relevant to neurodegenerative diseases, since this dicarboxylic acid has recently been implicated in the etiology of a number of neurologic disorders, including Huntington's disease, temporal lobe epilepsy, glutaric aciduria, and hepatic encephalopathy and coma.[17-23] Studies have demonstrated[12,13] that tryptophan loading in rats elevates brain tissue levels of quinolinic acid; concentrations of quinolinic acid in rat brain were elevated several-fold by a single injection of 300 mg/kg tryptophan. We have recently shown[15] that a single intraperitoneal injection of tryptophan (250 mg/kg) could elevate *extracellular fluid* levels of quinolinic acid in the brain approximately 200-fold. More physiologic doses of tryptophan (12.5 mg/kg, 50 mg/kg, and 100 mg/kg) led to increases of quinolinic acid of approximately 3-fold, 40-fold, and 80-fold, respectively, in the brain extracellular fluid compartment.[16] These same doses of tryptophan increased brain extracellular fluid levels of serotonin and its metabolites to only a minor extent (less than 2-fold at a dose of 100 mg/kg tryptophan). The levels of quinolinic acid obtained in these studies at the higher doses of tryptophan are equivalent to those shown to be toxic to neurons in vitro.[24]

Quinolinic acid and the NMDA (AA_1) receptor. Quinolinic acid toxicity in the brain appears to be mediated through its action as an agonist of the *N*-methyl-D-aspartate (NMDA) excitatory amino acid receptor.[25,26] Excitatory amino acid receptor subtypes in mammalian brain have been classified according to their respective affinities for structural analogues of glutamate: *N*-methyl-D-aspartate (AA_1), quisqualate (AA_2), and kainate (AA_3).[27,28] Unlike these analogues, quinolinic acid is an endogenous compound in human tissues, making its potential toxic action in the nervous system particularly relevant. Neurotoxicity induced by quinolinic acid occurs preferentially in the neocortex, striatum, and hippocampus, sites in the brain particularly affected by the CNS disorders mentioned above.[26,29] After injection directly into the brain, quinolinic acid produces axon-sparing lesions[30] similar to the pathology found in these disorders. Several antagonists to the NMDA receptor are presently under review as therapies for these and other neurologic disorders.[31-34]

Regulation of tryptophan and quinolinate metabolism. As shown in the figure, quinolinic acid is formed from a precursor, 3-hydroxyanthranilate, by the

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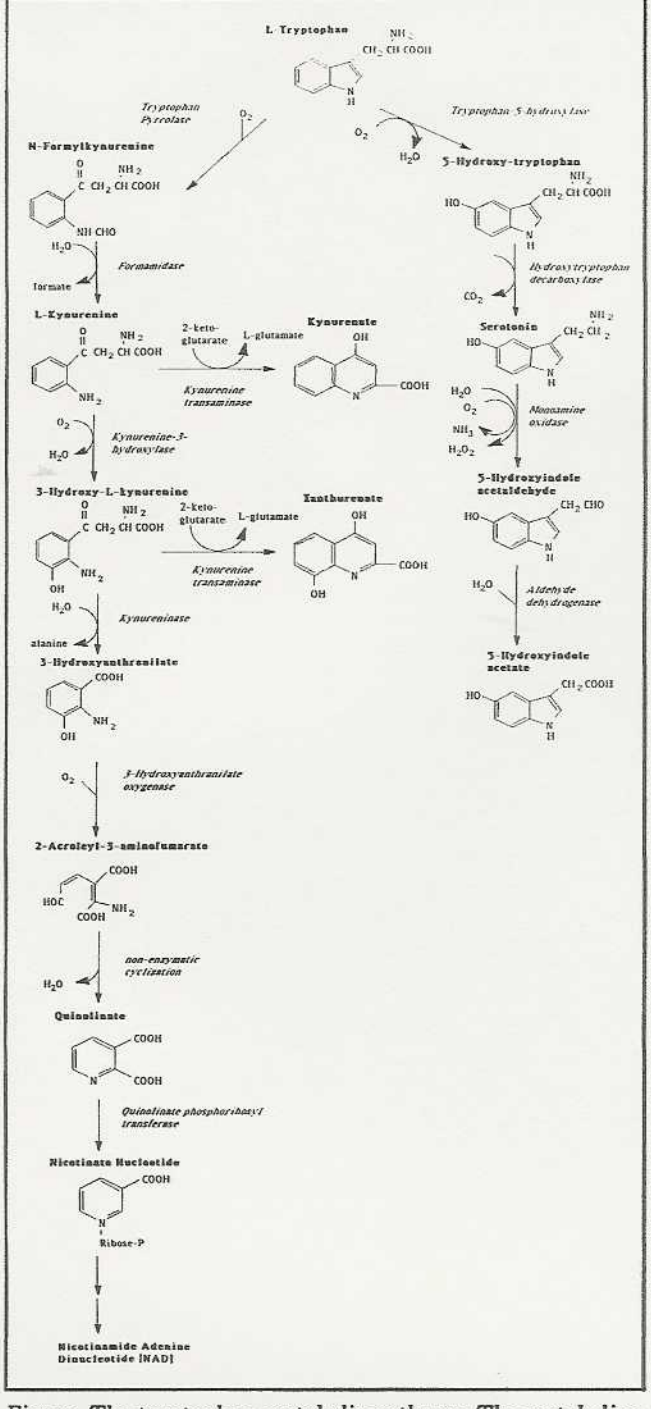

Figure. The tryptophan metabolic pathway. The metabolism of tryptophan splits between the indoleamine pathway producing serotonin and the kynurenine pathway producing quinolinic and kynurenic acids.

enzyme 3-hydroxyanthranilate oxygenase (3HAO); in turn, quinolinic acid is catabolized by the enzyme quinolinate phosphoribosyl transferase (QPRT).[35] Of particular importance is the finding that the maximal enzymatic rate (Vmax) for 3HAO is approximately 80-fold higher than that for QPRT, although the Michaelis Menten constant (Km) for both enzymes is about the same.[36,37] Thus, an increased flux of tryptophan into the kynurenine pathway could increase levels of quinolinic acid, which the degradative enzyme of quinolinic acid, QPRT, might be unable to remove. This possibility is supported by our findings that increases in quinolinic acid biosynthesis after a tryptophan load lead to markedly elevated extracellular fluid levels of the neurotoxin.[15,16]

Plasma, and hence brain, levels of tryptophan are regulated precisely. Human serum albumin binds tryptophan,[38,39] and the availability of tryptophan to cross the blood-brain barrier is determined by the amount of plasma free tryptophan. The albumin binding is saturable; therefore, elevated tryptophan intake can lead to elevated plasma levels of free tryptophan.[40] Furthermore, access of tryptophan across the blood-brain barrier is controlled by a specific large neutral amino acid transport system that transports all large neutral amino acids, including tryptophan, tyrosine, phenylalanine, valine, and isoleucine.[41] Thus, access of tryptophan to this carrier is determined by the ratio of levels of free tryptophan to all other neutral amino acids in plasma, rather than the level of free tryptophan in plasma alone.[38,42]

Tryptophan and quinolinic acid in neurologic disorders. *Huntington's disease.* In Huntington's disease, an autosomal dominant genetic disorder marked by choreoathetosis, a number of studies have suggested that a disorder in tryptophan metabolism may be present. Plasma levels of free tryptophan (versus bound to albumin) were elevated in 1 study[43]; in others, levels of other large neutral amino acids were decreased in the fasting state in Huntington's disease compared with controls.[44,45] Belendiuk's group[43] also demonstrated a direct correlation between plasma free tryptophan levels and the severity of chorea. Another study[46] found that daily feeding of tryptophan to juvenile Huntington's patients worsened their chorea, although the results of this study remain controversial.[47-49] Of considerable importance is the recent finding[50] that the brains of Huntington's disease patients have a 3- to 4-fold increase in the activity of the quinolinic acid-synthesizing enzyme, 3HAO, in the corpus striatum, the area in the brain most affected by this disease process. In contrast, the activity of the quinolinic acid-degrading enzyme, QPRT, is relatively unaffected in Huntington's disease.[37,51] All these studies suggest that Huntington's disease may prove to be caused by a disorder of the metabolism of tryptophan via the kynurenine pathway.

In addition, we have shown that when quinolinic acid is injected into the corpus striatum of rats and primates, a pattern of cell death results that is similar to that found in postmortem striatum of Huntington's disease victims.[23] In both the quinolinic acid-lesioned model and Huntington's disease, striatal levels of substance P-like immunoreactivity and gamma-aminobutyric acid are reduced, whereas levels of somatostatin-like immunoreactivity and neuropeptide Y-like immunoreactivity are spared, and in some cases increased.[23,52,53]

Another disorder that results in altered tryptophan metabolism, glutaric aciduria, also causes pathologic de-

struction of the corpus striatum and the clinical manifestation of choreoathetosis; in an animal model of glutaric aciduria, brain quinolinic acid levels were elevated.[12]

Hepatic disorders. Many severe hepatic disorders are associated with neurologic sequelae. Such effects constitute "hepatic encephalopathy," which can result from alcoholic cirrhosis, chronic hepatitis, or other liver disorders. Although the biochemical alterations responsible for hepatic encephalopathy remain poorly defined, 2 of the most consistent findings in both clinical cases and animal models are elevated blood and brain levels of ammonia and tryptophan.[54-60] Interestingly, ammonia facilitates the transport of tryptophan across the blood-brain barrier.[61] Liver failure is also associated with a marked increase in the plasma concentrations of unesterified free fatty acids, which compete with tryptophan for albumin binding sites.[62] Thus, increases in unesterified free fatty acids can increase plasma levels of free tryptophan, and as a result its access to the brain. In addition, hypoalbuminemia that can result from liver disorders would liberate otherwise bound tryptophan, permitting further increased delivery into the brain. An expected consequence of increased brain tryptophan levels would be augmented levels of brain quinolinic acid. Moroni et al[21,22] reported that quinolinic acid levels are increased in the CSF of patients suffering from hepatic encephalopathy or coma and in the brain parenchyma of animals with experimental liver damage.

Bucci et al[63] addressed the question of hepatic-related tryptophan neurotoxicity by chronically feeding rats 200 mg tryptophan/kg/d. In normal rats, no changes occurred in CNS morphology, but in rats with portocaval shunts (in which brain tryptophan delivery is further increased, as described above), histologic changes were noted. These changes included an increased number of enlarged astrocytes and neuronal nuclear and process degeneration in a variety of brain regions, including the caudate nucleus.

Other neurologic disorders. Alterations of the metabolism of tryptophan into kynurenines may also occur in a number of other disorders in which neurologic symptoms exist. Included among these are porphyrias, caused by metabolic defects in porphyrin synthesis or breakdown; neurologic sequelae are common. Porphyrin is the cofactor for the 1st enzyme in the kynurenine pathway, tryptophan pyrrolase, and alterations in porphyrin levels or structure could affect the activity and regulation of this enzyme.[64]

In addition, case reports have appeared in the literature that suggest the appearance of transient neurologic and psychiatric symptoms in patients receiving tryptophan doses ranging from 2 to 10 grams. Included among these symptoms are convulsive seizures, anxiety, and hyperirritability.[65-67] Other reports indicate behavioral side effects of tryptophan in combination therapy with other pharmaceuticals.[68-70] Some studies also suggest an association between inherited disorders of tryptophan metabolism and ataxia and developmental delay.[71-76]

Conclusion. Recent studies have suggested that the synthesis and release of neuroactive substances other than serotonin may be linked to tryptophan availability. Of these, quinolinic acid is particularly relevant, given its role as a potential neurotoxic agent in a variety of neurologic diseases as well as its agonist properties with respect to the NMDA (AA_1) receptor, implicated in the function of memory and learning through long-term potentiation.[77] The presence of quinolinic acid in the brain extracellular fluid compartment indicates that, although it is an intermediate metabolite in the intracellular conversion of tryptophan to NAD, quinolinic acid may play additional roles within the nervous system. Thus, it is possible that some behavioral and biochemical effects resulting from experimental alterations in tryptophan levels or metabolism in test animals may be due to changes in kynurenine pathway intermediates, rather than serotonin and its metabolites.

Of great interest is the observation that 2 kynurenine metabolites, quinolinic acid and kynurenic acid, have opposite effects on the NMDA receptor, the former acting as an agonist and the latter as an antagonist.[27] Kynurenic acid, therefore, can achieve a neuroprotective effect in the brain in the presence of excitotoxins such as quinolinic acid. However, when compared with quinolinic acid, kynurenic acid levels are far less responsive to acute tryptophan precursor loading; rat brain extracellular levels of kynurenic acid increased less than 10-fold following an intraperitoneal injection of 100 mg/kg tryptophan (unpublished observations). Also of interest, the tryptophan metabolite, serotonin, appears to modulate the sensitivity of the NMDA receptor for its agonists.[78]

Until a better understanding of the interaction among tryptophan, kynurenine pathway intermediates, and the NMDA receptor is achieved, perhaps caution should be exercised with respect to tryptophan self-medication by subsets of the general population.[79]

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