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L-Tryptophan: Biochemical, nutritional and pharmacological aspects

Review Article

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Summary. Tryptophan is important both for protein synthesis and as a precursor of niacin, serotonin and other metabolites. Tryptophan is an unusual amino acid because of the complexity of its metabolism, the variety and importance of its metabolites, the number and diversity of the diseases it is involved in, and because of its use in purified form as a pharmacological agent. This review covers the metabolism of tryptophan, its presence in the diet, the disorders associated with low tryptophan levels due to low dietary intake, malabsorption, or high rates of metabolism, the therapeutic effects of tryptophan and the side effects of tryptophan when it is used as a drug including eosinophilia myalgia syndrome.

Keywords: Amino acids – Tryptophan – Food – Eosinophilia myalgia syndrome

Introduction

Tryptophan is an essential constituent of the diet. It plays an important role in protein synthesis, and is also the precursor of a variety of biologically active compounds including serotonin, melatonin, tryptamine, quinolinic acid and kynurenic acid. In addition, tryptophan is a precursor to the coenzymes NAD and NADP, and can replace niacin as an essential nutrient. Both excessive intake and deficiency of tryptophan are detrimental to health. In the past, tryptophan has been used to treat several conditions, but it has now been withdrawn from the market in most countries, as some tryptophan preparations have been shown to cause the eosinophilia myalgia syndrome, a disease associated with muscle pain, eosinophilia and a variety of cutaneous,

neurologic and pulmonary symptoms. This survey covers the biochemistry of tryptophan, dietary tryptophan intake, the adverse effects of low tryptophan resulting from decreased intake or absorption, or increased metabolism of tryptophan, and the therapeutic effects of, and the adverse reactions to, tryptophan given as a drug.

Biochemistry and metabolism of tryptophan

L-tryptophan (tryptophan), an aromatic indolylpropionic acid (Fig. 1), was identified in 1901 by Hopkins and Cole. While other amino acids were isolated from acid digests of proteins, tryptophan is destroyed by heating in acid and was isolated from a tryptic digest, hence its name (Hopkins and Cole, 1901). It is one of the eight essential amino acids. Possibly because its concentration in the body is the lowest of all the amino acids, it can play a rate-limiting role in protein synthesis. Administration of tryptophan to mice increases aggregation of ribosomes in the liver and enhances protein synthesis (Sidransky et al., 1968), an effect that seems to be mediated by tryptophan binding sites on cell nuclei (Cosgrove et al., 1992). This enhancement of protein synthesis may have beneficial effects in some circumstances, as tryptophan reverses the ethanol-induced depression of albumin synthesis in rabbits (Rothschild et al., 1971), and also reverses some of the cirrhotic changes in the livers of rats treated intermittently with carbon tetrachloride (Sidransky et al., 1988).

In the mammalian brain, tryptophan is the precursor of serotonin (5-hydroxytryptamine). Serotonin seems to act as a trophic factor in the developing brain (Emerit et al., 1992), and is also a neurotransmitter. Serotonin has a modulatory role in neural information processing (Soubrié, 1986; Spoont, 1992). It is thought to inhibit a variety of behaviors including aggression, impulsivity, selection of food and alcohol, arousal, sexual behavior and reaction to pain. In addition, serotonin is involved in the control of mood. While serotonin is formed by hydroxylation and decarboxylation of tryptophan, direct decarboxylation of tryptophan leads to the trace amine tryptamine. Tryptamine is present in the brain at very much lower levels, but can modulate the action of serotonin on neurons (Boulton, 1979).

In the pineal, there is active synthesis of serotonin which is metabolized further to melatonin. Melatonin is secreted from the pineal gland actively during the night, and its synthesis is inhibited by light. It is involved in the regulation of diurnal rhythms, but can also influence reproductive and im-

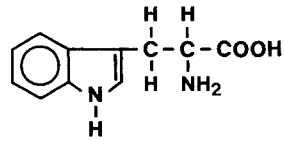

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Fig. 1. The structural formula of tryptophan

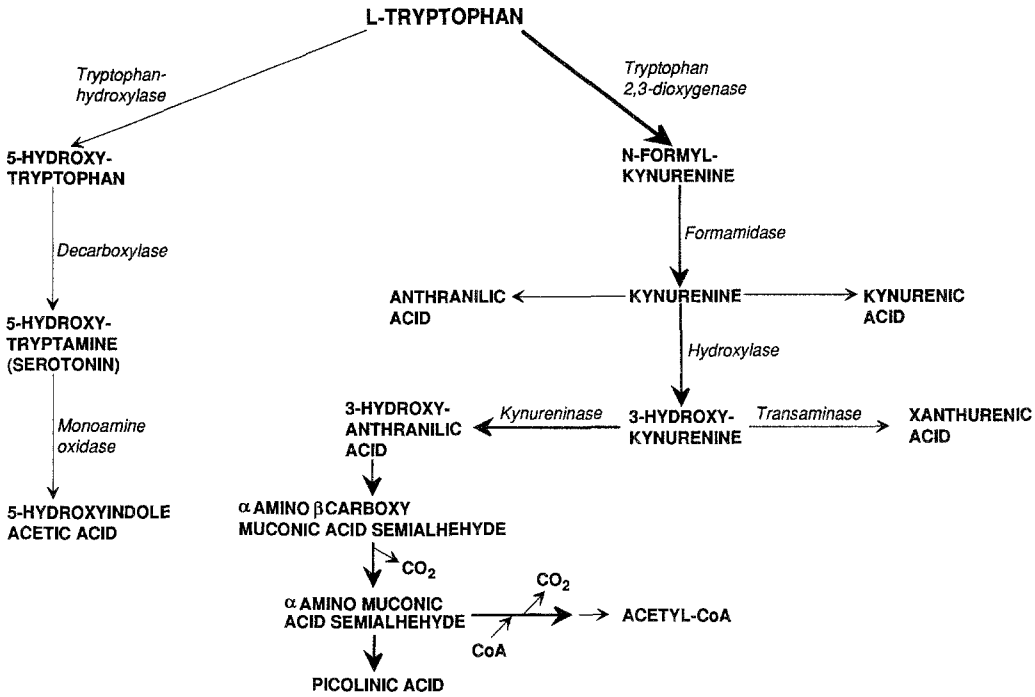

Fig. 2. Major pathways of tryptophan degradation in mammalians

mune functions (Reiter, 1991; Maestroni, 1993). A recent study suggests that administration of tryptophan to humans will increase blood melatonin levels (Huether et al., 1992a), an effect that may be mediated by melatonin synthesis in the intestine (Huether et al., 1992b).

Quantitatively the most important pathway for tryptophan metabolism, after protein synthesis, is the kynurenine pathway which is responsible for over 90% of tryptophan catabolism (Fig. 2). Two enzymes initiate this pathway, tryptophan-2,3-dioxygenase in the liver, and indoleamine-2,3-dioxygenase which is present in a variety of tissues. The former is induced by glucocorticoids and tryptophan (Knox, 1966; Sainio and Sainio, 1990). A variety of compounds that cause release of glucocorticoids, including nicotinamide, can induce this enzyme (Sainio and Sainio, 1990), but there is also some evidence, obtained in vitro, for feedback inhibition by niacin derivatives (Cho-Chung and Pitot, 1967). In the neonatal rat the activity of tryptophan-2,3-dioxygenase is not detectable, but its appearance can be induced prematurely with glucocorticoids (Yuwiler and Geller, 1973). Its activity varies with age, increasing in the postnatal period and decreasing again in old age (Segall and Timiras, 1983). Indoleamine-2,3-dioxygenase is present in a variety of tissues including the intestine, stomach, lungs and brain, and also macrophages and monocytes. It is induced by interferon gamma (Taylor and Feng, 1991).

The extent to which tryptophan is catabolized by tryptophan and indoleamine-2,3-dioxygenases varies in different species. Thus, in the rat, which has high levels of tryptophan-2,3-dioxygenase, administration of a glucocorticoid results in an increase in tryptophan catabolism. However, in

the gerbil, which has mainly indoleamine-2,3-dioxygenase, glucorticoids do not increase tryptophan catabolism (Green et al., 1975). In humans, glucocorticoids can increase the rate of tryptophan catabolism (Leklem, 1971) suggesting that tryptophan-2,3-dioxygenase is normally the main enzyme catabolizing tryptophan. However, when the immune system is stimulated there can be induction of indoleamine-2,3-dioxygenase by interferon gamma. In this situation degradation of tryptophan by indoleamine-2,3-dioxygenase may become important in humans (Fuchs et al., 1991; Pfefferkorn et al., 1986).

There are several important metabolites along the kynurenine pathway including kynurenic acid, which is an antagonist at glutamate receptors, and quinolinic acid which is a glutamate agonist (Moroni et al., 1990). The majority of tryptophan is eventually converted to carbon dioxide, but a small amount can act as a precursor of the coenzymes NAD and NADP (Krebs, 1971). In humans about 1mg of nicotinic derivatives is formed for each 60mg of tryptophan ingested (Horwitt et al., 1956; Horwitt et al., 1981). In developed countries the intake of tryptophan is probably usually high enough that little or no intake of niacin is required (see below). Thus, an intake of 900mg of tryptophan should result in the synthesis of about 15mg niacin, while a daily intake of 11 to 13mg niacin is adequate to prevent depletion of body stores of niacin (National Research Council, 1989).

Dietary tryptophan, plasma tryptophan and the brain

Tryptophan is the only amino acid bound to plasma albumin (McMenamy and Oncley, 1958). Part of the tryptophan bound to albumin is available for uptake into the brain (Yuwiler et al., 1977; Etienne et al., 1976). Various drugs including antirheumatic drugs such as salicylates and indomethacin, probenecid, chlorpromazine, diphenylhydantoin, tolbutamide, benzodiazepines, clofibrate (Lewander and Sjöstrom, 1973; Spano et al., 1974; Iwata et al., 1975; Müller and Wollert, 1975; McArthur et al., 1971b) and also free fatty acids (McMenamy, 1964) and bilirubin (McArthur et al., 1971a) can bind to the same binding site and affect the free (non-albumin bound) plasma tryptophan level. In some circumstances these compounds can cause small increases in brain tryptophan and serotonin as a result of the increase in the free plasma tryptophan (Curzon and Knott, 1974; Gessa and Tagliamonte, 1974). Another factor that has a greater effect on tryptophan uptake into brain is the plasma levels of the other large neutral amino acids (LNAA) (phenylalanine, tyrosine, leucine, isoleucine, valine, histidine, methionine and threonine) (Wurtman et al., 1981b). All these LNAA, including tryptophan, share a common transport system that moves them from blood to brain (Oldendorf and Szabo, 1976). All the LNAA compete for the carrier. The brain level of each of the individual amino acids will depend not just on the level of that amino acid in plasma, but also on the plasma levels of the other amino acids competing for the transport system.

When an animal ingests a protein meal plasma tryptophan will rise. However, because tryptophan is the least abundant amino acid in proteins the

plasma levels of the other LNAA will rise even more. As a result, the ratio of the level of tryptophan to the sum of the levels of the other LNAA in plasma (the plasma tryptophan ratio), as well as brain tryptophan and serotonin, will decline. After a carbohydrate meal, the plasma tryptophan level does not change. However, carbohydrate causes release of insulin which results in the net uptake of the branched chain amino acids, leucine, isoleucine and valine, into muscle. As a result, the plasma levels of the branched chain amino acids decline, the plasma tryptophan ratio increases, and the brain levels of tryptophan and serotonin rise (Sainio et al., 1991). Thus, meals containing tryptophan will tend to decrease brain tryptophan while meals containing no tryptophan will tend to raise brain tryptophan (Wurtman et al., 1981b), the opposite of what might intuitively be expected.

While protein and carbohydrate meals definitely alter brain serotonin in rats, the extent to which this occurs in humans is uncertain. After a lunch of starch or sugar the plasma tryptophan ratio is significantly higher than after a lunch of protein (Lieberman et al., 1986). However, in humans the changes that occur in the plasma tryptophan ratio are smaller than those which occur in the rat (Ashley et al., 1985; Teff et al., 1989a), and they are not necessarily seen at all times of day (Ashley et al., 1982). Therefore, the influence of these changes on human brain serotonin levels has been questioned (Teff et al., 1989b; Ashley et al., 1982). Furthermore, amounts of protein as small as 4% in a carbohydrate meal can block the rise in the plasma tryptophan ratio (Teff et al., 1989a). As few meals eaten by humans will contain less than 4% protein, serotonin mediated changes in behavior after carbohydrate meals are unlikely to be a normal physiological phenomenon.

The effects of carbohydrate and protein meals on levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA) in cerebrospinal fluid (CSF) have been studied in patients who had CSF taken for diagnostic purposes. Relative to a control water meal, a meal containing 100g of carbohydrate failed to have a significant effect on CSF tryptophan or 5HIAA. A meal containing 45g protein also did not affect CSF levels of tryptophan or 5HIAA, although it did cause a significant rise in CSF tyrosine (but not in CSF levels of the catecholamine metabolites homovanillic acid or 3-methoxy-4-hydroxyphenylethylene glycol). The increase in CSF tyrosine after a protein meal is consistent with animal data, as the increase in brain tyrosine when a rat ingests a protein meal is greater than any change in brain tryptophan after meals (Glaeser et al., 1983).

Overall the data suggest that protein and carbohydrate meals can affect brain serotonin in the rat. However, rats ingest a higher percentage of their body weight in food every day than do humans. As a result, changes in the plasma tryptophan ratio are smaller in humans than in rats, and meals probably do not affect human brain serotonin appreciably under most circumstances.

In the diet, foods which contain large amounts of protein such as cheese, fish, meat and eggs (Table 1) also contain abundant tryptophan (Souci et al., 1986). In common foods, the ratio of tryptophan to the sum of the LNAA is between 0.027 and 0.062. About 25% of the body's amino acid reserves consist

of these neutral amino acids while tryptophan accounts for 1–6%. Plasma levels of amino acids often change much less than dietary intakes of amino acids (Johnson and Anderson, 1982). Thus, differences in the intake of tryptophan and LNAA are unlikely to result in important variations in brain tryptophan and serotonin under normal circumstances.

Table 1. Consumption* of certain foods in Finland and the daily dietary intake**

Food	Consumption kg/year	Tryptophan content mg/100g	Daily tryptophan intake mg
Milk	173.3	42	199
Eggs	9.5	165	43
Wheat flour	15.5	110	47
Sausage	11.6	93	30
Potato	49.2	28	38
Cheese (Edam)	4.3	325	38
Beef	3.5	230	22

*The consumption figures are based on mean consumption figures issued by the Finnish Central Statistical Office (Central Statistical Office: Questionnare Study for Households in 1985, Helsinki 1988, 160 pages).
**The calculations of daily tryptophan intake are based on food consumption figures and the tryptophan contents of the foods concerned (Nutrion Tables, The Swedish National Food Administration, 1986, Liber Tryck Ltd., Stockholm).

Dietary intake of tryptophan in Finland

An adult requires 3.5mg tryptophan per kg body weight per day, or about 250mg per day, to maintain nitrogen balance (Harper and Yoshimura, 1993).

Table 2. The ratio of tryptophan content (TRP) to neutral amino acids (isoleucine, leucine, phenylalanine, tyrosine, valine) (SNA). Source: Souci, Fachmann, Kraut: Food Composition and Nutrition Tables, 1986/1987

FOOD	TRP	SNA	SNA/TRP
Eggs	230	4700	0.049
Milk	46	1130	0.041
Breast milk	22	400	0.055
Cheese	400	8780	0.046
Beans	27	503	0.054
Walnuts	170	3880	0.044
Tuna fish	300	6820	0.044
Pike	160	5770	0.027
Lobster	120	4480	0.027
Veal	310	6120	0.051
Champignon	24	460	0.052
Potato	30	480	0.062
Butter	9	242	0.037
Banana		16	
Pineapple	does not contain amino acids		

On the basis of food consumption figures (Table 2), the average dietary intake of tryptophan in Finland is about 900mg/day, well above the amount required. The main sources of dietary tryptophan are milk and other dairy products (309mg, which includes 74mg from cheese), meat and sausage (151mg), fish (57mg), white bread (47mg), eggs (43mg) and potatoes (38mg). The remaining 200 mg comes from other types of food. The average intake in Finland is 75% of the estimated intake from a hospital diet in the U.S.A. (Murphy et al., 1974).

Tryptophan deficiency and disease

Tryptophan and its metabolites are involved in many different types of pathology. However, in this review we cover only those conditions in which decreased availability of tryptophan may play some role in the symptomatology of the disorder. While the normal acute variations in dietary intake are unlikely to influence physiological functions via alterations in tryptophan availability, chronic dietary insufficiency can have important effects on health. One of the first biological treatments for a major psychiatric disorder was the dietary treatment of pellagra (Sebrell, 1981). Pellagra is caused by a deficiency of niacin. The symptoms of pellagra are usually described as consisting of diarrhoea, dermatitis and dementia, but the mental symptoms are much more varied than implied by the term dementia alone. Mild cases can be associated with headache, sleep disturbances and depression, while in more severe cases hallucinations, catatonia, dementia and seizures are all seen (Lehmann, 1972). Pellagra is associated with poverty and diets which rely heavily on corn, which is low in both niacin and its precursor tryptophan (Sebrell, 1981; Golberger and Wheeler, 1915). Pellagra resulting from diets high in corn can be avoided by treating the corn with alkali before cooking (e.g. as in boiling corn in lime water in the preparation of tortillas). The alkali increases the bioavailability of both tryptophan and niacin in the corn (Carpenter, 1981). Before the invasion of the American continent by Europeans all the different cultures of America that relied heavily on corn used alkali processing in its preparation (Katz et al., 1974). Newer varieties of corn have higher tryptophan and niacin contents and do not results in pellagra even in the absence of alkali processing (Xue-Cun et al., 1983).

Information on the effects of a specific tryptophan deficiency during human development come from a tragic incident in which tryptophan was left out of a commercially available dietetic formula being fed to children with phenylketonuria (Jaeger et al., 1979). Of the eighteen children who could be followed up the majority suffered from lethargy, loss of hair and skin lesions within six to eight weeks of starting on the defective diet. Other symptoms included loss of appetite, neurological disturbances and diarrhoea. While most of the symptoms resolved after the patients returned to an adequate diet, some of the neurological symptoms including visual impairment, optic atrophy, ataxia and spastic paresis of the legs persisted.

Defects in the absorption of tryptophan can influence health. Hartnup disease is an inherited autosomal recessive disease which results in deficient reabsorption of the neutral amino acids, including tryptophan, in the renal tubuli and also malabsorption of these amino acids in the gastrointestinal tract. The clinical manifestations of Hartnup disease are intermittent and variable. The deficient uptake of tryptophan can result in a pellagra-like condition, which may include mental manifestations such as nystagmus, ataxia, emotional lability, hallucinations and depression (Lehmann, 1972; Rosenberg and Scriver, 1974).

Another disorder in which absorption of nutrients from the gastrointestinal tract can be impaired is coeliac disease. Depression is one of the main causes of disability in undiagnosed coeliac disease (Hallert and Anström, 1982). In adults and children with coeliac disease the availability of tryptophan to the brain, as indicated by the plasma ratio of tryptophan to the sum of the other LNAA, is low especially in those with depression (Hernanz and Polanco, 1991; Hallert et al., 1982b). Low levels of the serotonin metabolite 5HIAA are found in the CSF of coeliac patients, but the levels of the dopamine metabolite homovanillic acid and of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylethylene glycol are also low (Hallert et al., 1982a) suggesting that low tryptophan availability may not be the only cause of the low CSF 5HIAA. When a group of coeliac patients were treated with a gluten-free diet for a year their CSF 5HIAA and tryptophan both increased, but the rise of 5HIAA (33%) was greater than that of tryptophan (10%) (Hallert and Sedvall, 1983). In another disorder associated with malabsorption, Crohn's disease, serum tryptophan was found to be low in some patients, but no attempt was made to relate this to any symptom except for weight loss (Beeken, 1976).

In a group of 24 patients with senile dementia tryptophan malabsorption was found in four patients using a tryptophan loading test (Lehmann, 1981). These patients were treated with tryptophan and 5-hydroxytryptophan for two to three weeks. Two patients showed improvement in their absorption of tryptophan and in their mental condition. The idea that malabsorption of tryptophan may play a role in the etiology of a small proportion of cases of dementia is intriguing and needs further research.

L-Dopa, like L-tryptophan, is a large neutral amino acid and may compete with tryptophan for transport systems. Parkinsonian patients who had been on dopa and who had shown psychotic symptoms had lower levels of tryptophan in all brain areas compared with those patients who did not develop psychoses (Birkmayer et al., 1974). In rats treated with dopa, administration of tryptophan normalizes the low levels of 5HT that are found (Fahn et al., 1975), and in patients tryptophan has been used successfully to alleviate the mental side effects that develop during dopa therapy (Birkmayer et al., 1972; Lehmann, 1973; Miller and Nieburg, 1974; Gehlen and Müller, 1974; Rabey et al., 1977). The side effect seen most often is psychosis, sometimes with hallucinations, but depression is also seen. In one study tryptophan failed to alleviate the dementia seen in Parkinsonian patients treated with dopa (Sweet et al., 1976). However, the dementia was probably a symptom of the

disorder rather than a side effect of the treatment. The mental symptoms associated with dopa therapy might be caused by inhibition of tryptophan uptake from the gastrointestinal system, as plasma tryptophan levels are lowered in dopa treated patients and are lowest in those with psychosis (Lehmann, 1973). Dopa inhibition of tryptophan uptake into the brain may also play some role (Young and Sourkes, 1977). However, it is not clear that the therapeutic effect of tryptophan in dopa-induced side effects is in fact due to restoration of tryptophan and 5HT levels. Tryptophan will inhibit dopa uptake and thus the effect of giving tryptophan may be similar to reducing the dose of dopa, a strategy likely to reduce side effects. Although tryptophan has no action by itself in Parkinson's disease, adding tryptophan to dopa therapy may have significant advantages over dopa alone even in patients who have no psychosis. When patients were treated with dopa and placebo or dopa and tryptophan, patients given the tryptophan showed a significant improvement in mood and drive, and possibly because of this their ability to do certain tasks showed significant improvement compared to those treated only with dopa (Coppen et al., 1972).

Overall the studies on patients with inadequate intake of tryptophan, due either to low levels in the diet or malabsorption, indicate that tryptophan deficiency causes a number of symptoms. These symptoms could be due to several factors, but decreased protein synthesis and low levels of niacin and 5HT are probably important in some of them. For example, low levels of 5HT may be involved in the etiology of depression (Meltzer and Lowy, 1987), and depression is associated with many of these conditions.

Low levels of tryptophan could be caused either by low levels of tryptophan in the diet, tryptophan malabsorption, or by excessive metabolism of tryptophan. Normally only about 1% of ingested tryptophan is excreted in the urine as 5HIAA. However, in patients with the carcinoid syndrome this can increase to as much as 60% (Sjoerdsma et al., 1956). Although mental symptoms have only rarely been reported in the carcinoid syndrome, there is a series of case reports with symptoms that include emotional lability, depression, confusion, hallucinations, and stupor. In five patients with these symptoms plasma tryptophan was measured and found to be very low. Three of these patients were treated with tryptophan and all showed an improvement in their mental state (Lehmann, 1972).

The main catabolic enzyme for tryptophan is tryptophan-2,3-dioxygenase, an enzyme that is induced by cortisol in humans (Altman and Greengard, 1966). In Cushing's syndrome there is excessive excretion of cortisol and depression is often seen. However, in patients with active Cushing's syndrome plasma tryptophan was reduced by only 10% compared with plasma tryptophan in patients with Cushing's syndrome who had been treated (Kelly et al., 1980). This suggests that induction of tryptophan-2,3-dioxygenase by cortisol is not of sufficient magnitude to cause a marked reduction in plasma tryptophan. Thus, symptoms of depression in Cushing's syndrome are not due to decreased tryptophan availability.

While induction of tryptophan-2,3-dioxygenase by cortisol may not play a role in psychopathology, induction of indoleamine-2,3-dioxygenase by

interferon gamma may have pathophysiological significance. In patients with HIV infection the immune activation is associated with elevated interferon gamma. In such patients tryptophan levels are low in plasma and CSF and are correlated with neopterin levels. Neopterin levels are an indicator of immune activation and are correlated positively with interferon gamma levels (Fuchs et al., 1990a). The low tryptophan levels are accompanied by high kynurenine levels (Fuchs et al., 1991), and show a significant association with neurological and psychiatric symptoms, mainly dementia and polyneuropathy (Fuchs et al., 1990b). The decline in tryptophan availability seems to be accompanied by a decline in CNS serotonin synthesis. Thus, while patients with HIV infection and symptoms at Center for Disease Control (CDC) stage III had normal CSF 5HIAA levels, patients at the more advanced CDC stage IV had low CSF 5HIAA even though their CSF homovanillic acid, dopamine and noradrenaline levels were normal (Sofic et al., 1992). Whether low tryptophan levels contribute to the symptomatology of HIV patients is unclear. Low serotonin might contribute to depression, particulary in susceptible subjects. Low protein synthesis is another possible mediating mechanism, but low niacin levels will not occur because induction of indoleamine-2,3-dioxygenase will increase flux along the pathway to niacin. One metabolite of interest along this pathway is quinolinic acid, which is an agonist at glutamate receptors and can cause neuron death at high concentrations. In patients with HIV infection both CSF and brain quinolinic acid levels are elevated (Achim et al., 1993). In the early stages of the disease CSF quinolinic acid levels were elevated two fold, but in patients with overt AIDS dementia complex it was elevated over 20 fold (Heyes et al., 1991). However, it not clear to what extent any of the changes in tryptophan metabolism are responsible for the symptomatology or are merely reflecting immune activation.

Because of the interest in low serotonin levels in the etiology of depression several groups have looked at plasma tryptophan levels or the plasma ratio of tryptophan to the other LNAA in depressed patients. Values are often found to be low in depression, e.g. (Maes et al., 1990; DeMeyer et al., 1981; Dunlop et al., 1983; Lucca et al., 1992; Joseph et al., 1984). However, the magnitude of the decline is too small to cause an appreciable decline in brain serotonin, and it is unlikely that reduced tryptophan availability is involved in the etiology of most cases of depression. Nonetheless, a low plasma tryptophan ratio is capable of predicting the response to a variety of different antidepressant drugs (Moller, 1990).

Medical uses of tryptophan

The rationale for the therapeutic use of tryptophan depends on the fact that alterations in brain tryptophan levels can influence serotonin synthesis. This is because in humans (Young and Gauthier, 1981) as in rats (Fernstrom and Wurtman, 1971) brain tryptophan hydroxylase is only about half saturated with its substrate. Increases in tryptophan availability can double the rate of

serotonin synthesis but will not increase it any more than that (Young and Gauthier, 1981). The first study using tryptophan to influence mood was published in 1958 by Lauer et al. (1958) who gave L-tryptophan (20mg/kg/day for 6 weeks) to seven schizophrenic patients who were receiving a monamine oxidase inhibitor. They noted that "the patients exhibited an increase in energy level and motor activity and improvement in the ability to accept interpersonal relationships, and displayed more affect". Numerous other studies have tested the therapeutic effect of tryptophan in a variety of disorders over the past 35 years. One of the attractions of this approach is that it has both theoretical significance, because tryptophan is relatively specific for its effects on serotonin, and practical significance because tryptophan, being a dietary component, is, with certain notable exceptions, a safe drug even at doses up to 12g per day. The efficacy of tryptophan in depression and other psychiatric disorders has been reviewed (Young, 1986; Cole et al., 1980; Baldessarini, 1984; Young, 1990; Boman, 1988).

The consensus about the antidepressant effect of tryptophan is that it is not as effective as a standard antidepressant in severely depressed inpatients (Young, 1986; Cole et al., 1980; Baldessarini, 1984). However, one of the better clinical trials of tryptophan in depression was conducted on mild to moderately depressed outpatients, and concluded that tryptophan (3g/day) was more effective than placebo, and as effective as amitriptyline (Thomson et al., 1982). Tryptophan produced no more side effects than placebo, and significantly fewer side effects than amitriptyline. One small study indicates that tryptophan is significantly better than placebo in the treatment of Seasonal Affective Disorder (McGrath et al., 1990). This interesting observation needs confirmation.

Several early studies suggest that tryptophan can potentiate the antidepressant effect of monoamine oxidase inhibitors. However, it also tends to potentiate the side effects of these drugs and the combination is usually used only in treatment-resistant patients. While tryptophan potentiates the action of monoamine oxidase inhibitors, it does not seem to potentiate the action of other antidepressant treatments such as tricyclic antidepressant and electroconvulsive therapy (Young, 1991).

Because of clinical studies suggesting that aggressive patients have low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA) in their cerebrospinal fluid (CSF) (Virkkunen et al., 1989; Coccaro, 1992), two studies have investigated the possible effect of tryptophan in pathologically aggressive patients. In the first, which was performed on aggressive schizophrenics, tryptophan caused a significant reduction in uncontrolled behavior relative to placebo (Morand et al., 1983). In the second study, on aggressive psychiatric inpatients, tryptophan did not decrease aggressive acts, relative to placebo. However, the patients required significantly less neuroleptic medication to control their aggression when they were on tryptophan (Volavka et al., 1990).

Several studies have investigated the efficacy of tryptophan in clinical pain. King (1980) reported that tryptophan relieved the pain of patients in whom chronic pain had recurred after successful treatment by rhizotomy or

cordotomy. While this study was uncontrolled, patients continued the treatment for periods up to 13 months, and patients with longstanding pain tend to withdraw from treatment if it is ineffective. In a controlled trial, Seltzer et al. (1983) found tryptophan to decrease clinical pain in patients with chronic maxillofacial pain. Tryptophan has also been reported to reduce pain 24 hours after endodontic surgery (Shpeen et al., 1984). While some of the clinical studies with tryptophan have revealed therapeutic effects, others have not. In patients with spinal disk disease, no effect of tryptophan was found (Sternbach et al., 1976). Tryptophan was also ineffective when given at bedtime in patients with the fibrositis syndrome (Moldofsky and Lue, 1980). In a recent study, tryptophan given pre- and postoperatively did not effect pain development or analgesic consumption after third molar surgery (Ekblom et al., 1991). Finally, in two studies on pain after abdominal surgery, intravenous tryptophan infusions failed to decrease pain or morphine requirements (Franklin et al., 1990; Ceccherelli et al., 1991). In the first of these studies (Franklin et al., 1990) patients with lower levels of tryptophan tended to require less morphine, in contrast to an experimental study using the cold pressor test which showed that lowered tryptophan levels abolished morphine analgesia (Abbott et al., 1992). The varying results obtained with tryptophan in different types of clinical pain probably reflect the fact that the word pain includes physiological phenomena acting through a variety of different mechanisms. Ths situation in which tryptophan has shown a therapeutic effect most frequently is chronic pain associated with deafferentation or neural damage.

Tryptophan, given for several weeks, has been tested against placebo in two clinical studies to see if it would decrease total calorie or carbohydrate intake of obese and/or carbohydrate craving subjects (Wurtman et al., 1981a; Strain et al., 1985). In neither of these studies was there any effect on weight or food selection of the patients. In a single study, a mixture of L-tryptophan, DL-phenylalanine, L-glutamine and pyridoxal phosphate helped weight loss in carbohydrate carving subjects (Blum et al., 1990). However, the open design and the mixture of compounds given make the results of this study difficult to interpret.

Tryptophan has been tested as a hypnotic in nearly 50 studies. Although results are rather variable, the consensus of reviews of this area is that tryptophan can be an effective hypnotic under some circumstances (Young, 1986; Hartmann and Greenwald, 1984; Cooper, 1979; Boman, 1988). While tryptophan is not as effective as standard hypnotics in severe insomnia, it can decrease sleep latency by about half in mild insomnia. At lower doses (<4g) it does this without altering sleep architecture.

Tryptophan increased exercise performance relative to placebo, an effect that the authors suggested might be due to an analgesic effect (Segura and Ventura, 1988). However, in a second study tryptophan did not improve running performance (Stensrud et al., 1992).

A single case report suggests a therapeutic effect of tryptophan in nonketotic hyperglycinemia (Matsuo et al., 1995), a rare genetic disorder. Tryptophan increased the levels of the tryptophan metabolite kynurenic acid

in the CSF. The interesting aspect of this case report is that the therapeutic effect of tryptophan was attributed to the inhibitory effect of kynurenic acid on excitatory amino acid receptors, rather than to an increase in serotonin levels.

The clinical studies on tryptophan have established a therapeutic effect in mild to moderate depression and insomnia and have pointed to a number of promising areas (particularly pain and aggression) where more studies are needed.

Toxicology of tryptophan

The daily dietary intake of tryptophan can be up to 1 g and doses of less than 1 g taken in addition to the normal dietary intake are unlikely to cause any adverse effects. Small doses are often used in the treatment of mild insomnia, as tryptophan is no more effective at higher doses than at 1 g (Hartmann et al., 1974). However, as an antidepressant tryptophan has been used at a daily dose of from 3 to 12 g, which obviously raises greater concern. In the rat tryptophan has the lowest LD_{50} of any amino acid, 1.6 g/kg (Gullino et al., 1956). At this dose symptoms of toxicity appeared between 10 minutes and 2 hours after ingestion. Death, which was probably due to the accumulation of metabolites such as urea and ammonia, occurred between five hours and three days. Autopsies performed on animals that survived an LD_{50} dose showed no evidence of pathology, either gross or microscopic (Gullino et al., 1956). A dose of 1.6 g/kg is equivalent to an intake of over 100 g for a 70 kg human. As much smaller doses taken orally would induce vomiting it is unlikely that a human could commit suicide with tryptophan.

Doses below the LD_{50} reduce food intake and growth of rats when given chronically. This is not specific to tryptophan, but occurs with any diet in which there is an imbalance of any amino acid. The adverse effects of amino acid imbalance are exacerbated by diets low in protein and diminished by diets high in protein (Harper et al., 1970). Thus, patients taking any amino acid supplement should always be sure to ingest adequate amounts of protein.

The literature contains a variety of reports of adverse effects of tryptophan in experimental animals. These include fatty liver and ultrastructural changes in the liver of rats (Hirata et al., 1967; Trulson and Sampson, 1986), cytoskeletal and macromolecular permeability alterations in hamster small intestinal epithelium (Madara and Carlson, 1991), acute hemolytic anemia in ponies (Paradis et al., 1991), enhancement of plasma lipid peroxidation in rats (Aviram et al., 1991), and fibrosis and acinar changes in the pancreas (Love et al., 1993). The last of these is of interest because tryptophan levels in the pancreas are five times higher than in the liver (Sainio et al., 1991). However, the literature on the adverse effects of tryptophan is not always consistent. For example, while tryptophan many enhance lipid peroxidation in rats (Aviram et al., 1991), both tryptophan and some of its oxidative metabolites are efficient scavengers of peroxyl radicals and inhibit peroxyl radical mediated

oxidation of lipid (Christen et al., 1990). Also, tryptophan was not found to cause fatty liver or ultrastructural changes in rats in a recent study (Matthies and Jacobs, 1993), and it alleviates fatty liver in laying hens (Akiba et al., 1992). While the studies mentioned above usually involved short term administration of tryptophan, a large and long term study was carried out under the aegis the National Cancer Institute in the U.S.A. (National Cancer Institute, 1978). Large groups of rats and mice were given greatly elevated amounts of tryptophan in their diets for most of their lives. Not only was there no increased incidence of cancer, but inspection of the tissues at autopsy revealed no gross or microscopic changes. Obviously considerable weight should be given to the findings from this study because of its size and length.

When tryptophan was freely available as a dietary supplement it was often viewed as a "natural" treatment of disorders such as insomnia, and therefore might have been used by pregnant women. Thus, work on the possible adverse effects of tryptophan on pregnancy is of great interest. Tryptophan, given as 1.8% of the diet of pregnant hamsters, caused a significant reduction in embryo and neonate survival and in neonatal weight of the pups (Meier and Wilson, 1983), an effect possibly mediated by the peripheral vasoconstrictive effect of 5HT. However, a ten-fold increase of tryptophan in the diet of pregnant rats had no adverse effect (Funk et al., 1991). Increasing tryptophan in the diet 25-fold resulted in decreased maternal weight gain, but this might be expected with any severe amino acid imbalance. Adverse effects of tryptophan in pregnancy may not be limited to effects on fetal weight. Administration of tryptophan-enriched diets to pregnant rats retards the development of the 5HT system in their offspring (Huether et al., 1992c). Although it is not known whether moderate supplementation with tryptophan has any effect on the human fetus, tryptophan should not be given to pregnant women unless the therapeutic gains outweigh the risk of adverse effects to the fetus.

The literature has very few reports of adverse effects when pure tryptophan supplements are given to humans (Young, 1986; Sourkes, 1983) even though tryptophan has been used experimentally for over 30 years and clinically for over 20 years. However, animal studies suggests several situations in wich tryptophan should be used with caution. The first is pregnancy. The second is related to the possible carcinogenicity of tryptophan metabolites. Thus, 3-hydroxyanthranilic acid, and some other metabolites along the kynurenine pathway, cause bladder cancer when they are implanted in pellet form in the bladder of rats (Bryan, 1971). Given that tryptophan supplementation does not seem to cause cancer in the rat (National Cancer Institute, 1978), a possible carcinogenic effect of tryptophan should only be of concern to those patients with a source of physical irritation in the bladder similar to that caused by the pellets of 3-hydroxyanthranilic acid. A third area of concern is the diabetogenic effect of the tryptophan metabolite xanthurenic acid, which is increased on tryptophan loading (Wolf, 1974). This effect is possibly due to the ability of xanthurenic acid to bind insulin (Ikeda and Kotake, 1984; Hattori et al., 1984). Caution should be used when giving

tryptophan to patients with a family history of diabetes. Fourth, in ruminants oral tryptophan causes marked pulmonary edema and emphysema. This seems to be due to bacterial conversion of tryptophan to skatole (3-methylindole), which causes the same type of lung lesions (Carlson et al., 1972). Fifth and last, animal data suggest that photooxidation of tryptophan and some of its metabolites, such a kynurenine, are involved in cataract formation (Zigman, 1984). Although no such evidence exists for humans, tryptophan administration is likely to raise lenticular tryptophan and kynurenine concentrations, and this might make subjects more susceptible to cataract formation, particularly if exposed to ultraviolet light.

The most common adverse effect reported when tryptophan is given to humans is the serotonin syndrome. The serotonin syndrome was first described in rats. When these animals are given tryptophan plus a monoamine oxidase inhibitor (MAOI), or various other drugs including high doses of 5-hydroxytryptophan with a peripheral decarboxylase inhibitor, or serotonin receptor agonists, the animals exhibit tremor, rigidity, hypertonicity, hind-limb abduction, rigidly arched tail, lateral head shaking, treading movements of the forelimbs, hyperreactivity, myoclonus and even generalized seizures (Gerson and Baldessarini, 1980). The appearance of the serotonin syndrome in 38 patients in 12 reports has been reviewed recently in two reviews (Sternbach, 1991; Lejoyeux et al., 1994). The majority of these cases were associated with a combination of tryptophan and an MAOI, but the combination of a serotonin uptake inhibitor and MAOI can also cause the serotonin syndrome. The main symptoms seen were changes in mental status including confusion and hypomania, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor. The incidence of the serotonin syndrome in patients is unknown, but Sternbach (1991) argues that it is underreported, because it is not recognized, or because it is confused with the neuroleptic malignant syndrome, which has some similarities in terms of symptoms.

The serotonin syndrome usually resolves within 24 hours of cessation of tryptophan treatment, with no residual symptoms. The animal model suggests that serotonin antagonists should be a useful treatment, and a single case report suggests the efficacy of cyproheptadine (Lappin and Auchinloss, 1994). Supportive measures have been used including cooling for hypothermia, intramuscular chlorpromazine as an antipyretic and sedative, artificial ventilation for respiratory insufficiency, anticonvulsants for seizures, clonazepam for myoclonus and nifedipine for hypertension (Sternbach, 1991).

Although the combination of tryptophan and fluoxetine, a specific serotonin reuptake inhibitor, has been reported to produce the serotonin syndrome in some patients (Steiner and Fontaine, 1986), the combination of tryptophan and tricyclic antidepressants usually does not lead to any more side effects than the tricyclic antidepressant alone (Young, 1986). Indeed, in the largest study of the combination of tryptophan and a tricyclic antidepressant, the increase in heart rate seen with amitriptyline was less marked in the combined treatment group (Thomson et al., 1982). However,

the production of the serotonin syndrome with fluoxetine suggests that all specific serotonin uptake inhibitors should be used with caution in conjunction with tryptophan.

Tryptophan alone seems to produce no more side effects than placebo when given at a moderate dose (3g per day) (Thomson et al., 1982). In studies using higher doses of tryptophan, 9.6g per day in affective disorder patients (Murphy et al., 1974), and 20g per day in schizophrenic patients (Gillin et al., 1976), no side effects were noted. In studies in which side effects are noted they are generally mild, the most common being nausea and lightheadedness (Young, 1986).

While tryptophan itself seems to be relatively safe, during cooking of protein containing foods tryptophan forms various pyrolysis products which are mutagens, carcinogens and comutagens. The structure of some of these compounds have been isolated after pyrolysis of pure tryptophan and they are all indole containing compounds (Friedman and Cuq, 1988; Fujiki et al., 1984). Similar carcinogenic pyrolysis products of tryptophan have been detected in human bile (Manabe and Wada, 1990) suggesting that the normal daily diet contains carcinogenic tryptophan pyrolysis products. Their toxicological significance have not yet been established in humans. However in hamsters some of these compounds have an LD_{50} as low as 50mg/kg (Friedman and Cuq, 1988).

Eosinophilia myalgia syndrome

In late 1989 an epidemic of a new disorder appeared in the U.S.A. It came to be called the eosinophilia, myalgia syndrome (EMS). EMS is an inflammatory syndrome characterized by eosinophilia, myalgia, periomyositis, fascitis and neuropathies. It was apparently caused by several lots of L-tryptophan manufactured by a single company, Showa Denko K.K. In the U.S.A. there were over 1500 cases and 38 deaths. EMS occurred in various European countries and Japan also, but there were not as many cases as in the U.S.A. (Swygert et al., 1990; Belongia et al., 1990; Silver et al., 1990; Mizutani et al., 1991; Belongia et al., 1992; Hertzman et al., 1990; Kilbourne et al., 1990; Castot et al., 1991; Carr et al., 1994). In Canada, where tryptophan is on the market as a prescription drug and the original source of the tryptophan was not Showa Denko K.K., there were no cases of EMS associated with the use of tryptophan as a prescription drug. However, as many as ten cases of EMS were reported in Canada due to individuals buying tryptophan over the counter in the U.S.A. (Wilkins, 1990). Canada is one of the few countries where tryptophan is still available for human use. Another is Finland, where no cases of EMS have been reported. In Finland, as in Canada, tryptophan has been banned only as a food additive (Finnish National Board of Health circular of 21.12.1989). It can still be prescribed as a drug. Recently tryptophan has been reintroduced into Britain as a prescription drug (Lader, 1994).

The exact cause of EMS is still unclear. Chemical analysis of lots of tryptophan associated with EMS revealed numerous minor contaminants.

The early focus was on 1,1'-ethylidenebis(L-tryptophan), also know as EBT, "peak 97" and "peak E" (from peaks obtained on high performance liquid chromatography) (Belongia et al., 1990; Crofford et al., 1990; Mayeno et al., 1990; Smith et al., 1991). However, recent epidemiological data suggest that some lots of tryptophan not associated with EMS have levels higher than some lots associated with EMS. While lots associated with EMS had higher EBT levels overall, the difference between the level of EBT in lots associated and not associated with EMS did not reach the 0.05 level of significance ($p = 0.12$) (Philen et al., 1993). Other chemical contaminants could be responsible for EMS, or could modify the effects of EBT. Another recent study found more than 60 minor contaminants in tryptophan from Showa Denko K.K. Six of the contaminants showed a significant association with lots found to cause EMS. The six compounds were EBT, 2(3-indolymethyl)-L-tryptophan, 3-anilino-alanine and three other compounds of unknown structure (Hill et al., 1993). The discovery of 3-anilino-alanine as a case-associated contaminant is of interest because of the similarities of EMS to the toxic oil syndrome (TOS). TOS occurred in 1981 in Spain and affected 10,000 people, 800 of whom died. It was probably due to the addition of aniline to cooking oil (World Health Organization, 1992). However, while the discovery of an aniline-derivative in case-associated lots of tryptophan strengthens the idea of an association between EMS and TOS, the compound(s) responsible for TOS has never been discovered.

Not all subjects who ingested tryptophan manufactured by Showa Denko developed EMS, with different studies finding rates that vary widely (Belongia et al., 1990; Kamb et al., 1992). Dose of tryptophan is probably an important factor, with one study finding rates of EMS above 50% when the dose was 4 g per day or higher (Kamb et al., 1992). Patients on tryptophan often received antidepressant drugs that inhibit drug metabolism via cytochrome P450. This fact led to a study of the pharmacogenetic characteristics of EMS (Flockhart et al., 1994). Patients with EMS were found to have a significantly elevated incidence of a P450 genotype associated with low rates of metabolism. This raises the possibility that exposed individuals who were protected from EMS were able to metabolize the contaminant(s) associated with EMS better than those who developed the disorder.

The epidemic of EMS starting in 1989 focussed attention on ingestion of tryptophan, and led to suggestions that isolated cases of eosinophilic fascitis may have occurred in people ingesting tryptophan before the epidemic and before the contaminated lots of tryptophan were manufactured (Hibbs et al., 1992; Blauvelt and Falanga, 1991). Isolated cases resembling EMS have also been reported without ingestion of tryptophan (Bochner et al., 1991; Clauw et al., 1994), or after ingestion of 5-hydroxytryptophan (5-HTP) (Hornstein et al., 1989; Auffranc et al., 1985; Sternberg et al., 1980; Michelson et al., 1994). Although there is no data available yet on possible contaminants in 5-HTP, condensation between 5-HTP and acetaldehyde can form a tetrahydro-β-carboline, while exposure of EBT to acidic conditions similar to those found in the stomach results in several products including a tetrahydro-β-carboline (Ito et al., 1992).

The confusion concerning the possible etiology of EMS resulting from the clinical data has not been dispelled by animal work. When Lewis rats were fed tryptophan from lots that were definitely associated with EMS they showed periomyositis and fascitis (Crofford et al., 1990). EBT alone caused significant myofascial thickening, but only at doses well above those likely to be ingested by subjects taking tryptophan. However, in the same study, lots of tryptophan not associated with EMS were found to cause mild but significant myofascial thickening (Love et al., 1993). Tryptophan has also been reported to cause eosinophilia to animals with adrenal dysfunction (Shishikura et al., 1991; Sato et al., 1992).

It remains unclear what compound or compounds are responsible for EMS, whether they act alone or in conjunction with tryptophan, and whether metabolic factors predisposed some individuals to EMS. Treatment of EMS is completely symptomatic and often includes a glucocorticoid (prednisolone). However, many patients do not respond adequately to treatment (Kaufman et al., 1991).

Conclusion

Tryptophan is unique as a component of the diet as it plays an important role in protein synthesis and is also the precursor of a variety of important metabolites including niacin and serotonin. As a drug it is not widely used, but may be therapeutic in some circumstances. The important distinction between tryptophan in the diet and as a drug is not always made clearly in the literature. Articles refer to the "dietary" use of tryptophan when it is being used as a supplement in purified form. There are a number of reasons why the word "dietary" is not appropriate in this context. First, as tragically illustrated by the EMS epidemic, when supplemental tryptophan is given it is a manufactured product, not a component of the diet. Second, when supplemental tryptophan is given it causes an amino acid imbalance, and in the absence of other amino acids will not be a substrate for protein synthesis. Third, some of the metabolic effects of tryptophan are different when it is given as part of the diet and as a drug. Thus, tryptophan as a component of the diet will not raise brain tryptophan and serotonin levels because of competition between tryptophan and the other large neutral amino acids for entry into the brain. This does not occur when tryptophan is ingested by itself and supplemental tryptophan will raise brain serotonin. Thus, there is a clear distinction between ingestion of tryptophan in the diet and as a drug.

One of the major conclusions of this review is that in spite of many decades of work on tryptophan there still remain many research opportunities. This is especially true concerning the therapeutic effect of tryptophan, but also as far as dietary and metabolic effects are concerned.

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