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DISEASES ASSOCIATED WITH DEFECTS IN VITAMIN B_6 METABOLISM OR UTILIZATION

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INTRODUCTION

Pyridoxal 5'-phosphate (PLP) is a cofactor for enzymes catalyzing transaminase, decarboxylase, and synthetase reactions (among others) in pathways spanning carbohydrate metabolism, sphingolipid biosynthesis and degradation, amino acid metabolism, heme biosynthesis, neurotransmitter biosynthesis, and in the pathways for many other important biomolecules. Several methods have been suggested to identify deficiencies of this vitamin and assess human requirements. These include measuring fasting plasma PLP (84), urinary pyridoxic acid (139), stimulation of various serum and erythrocyte aminotransferases by PLP (169), and urinary metabolites of pathways sensitive to depletion of vitamin B_6 (76). Based on these parameters, vitamin B_6 status has been observed to differ among humans of different nutritional conditions (e.g. 5, 109), age (73), degree of activity (29, 77), and varying types of diseases (56, 127, and this review).

Since there is currently no consensus on the best biochemical marker for humans, this confuses assessment of B_6 status in disease. Plasma PLP is most often studied, and is a reasonable indicator of human vitamin B_6 status, but Lui et al (79) suggest that plasma PLP content is a good indicator of the body store whereas pyridoxic acid is a better indicator of intake. Many diseases are also affected by pyridoxine supplements even though the role of aberrant vitamin B_6 metabolism in their etiology has not been investigated. Hence, this review covers both diseases that are known to affect utilization of vitamin B_6 and some in which a link has only been suggested.

VITAMIN B_6 METABOLISM AND UTILIZATION BY HUMANS

The overall handling of vitamin B_6 (e.g. digestion, absorption, transport, metabolism, storage, and excretion) was recently reviewed by Ink & Henderson (56) and in proceedings from vitamin B_6 symposia (127). A brief overview of these topics, with some update from recently conducted studies with humans, is given as background.

Intake, Transport, and Metabolism

Vitamin B_6 is obtained from various dietary sources, although bioavailability can vary considerably (41). Foods contain varying proportions of the three vitaminic forms pyridoxine, pyridoxamine, and pyridoxal. Pharmacologic formulations of vitamin B_6 include pyridoxine and pyridoxine hydrochloride in various dosages (e.g. 4 to 100 mg/tablet). Unfortunately, pyridoxine is also sold by some health food stores in up to 1-g tablets, which is well above the dosages that can result in peripheral neuropathy (122, 137).

After intestinal absorption (105), most is transported to liver and taken up by facilitated diffusion. After being phosphorylated by pyridoxal kinase (64, 90, 96), pyridoxine- and pyridoxamine 5'-phosphates are converted to PLP by a flavin-dependent oxidase (58, 149). Pyridoxal 5'-phosphate is bound by apo-enzymes, or released into plasma and carried to tissues as a tight complex with albumin (25). Pyridoxal is also associated with red blood cells, where it is tightly bound by hemoglobin (97).

Upon hydrolysis by alkaline phosphatase (81), free pyridoxal is taken up by cells and rephosphorylated (for muscle as an example, see 11). Pyridoxal is also oxidized to pyridoxic acid by hepatic and renal aldehyde oxidases and a pyridoxal dehydrogenase (155). In humans, it appears that the oxidase is mainly responsible for pyridoxal degradation (100).

The regulation of vitamin B_6 metabolism involves contributions by several key enzymes and binding proteins, as well as transport of PLP to major tissue sites of metabolism. In humans, as has been shown in many mammalian systems (56), the relatively high activity of hepatic pyridoxal kinase results in rapid conversion of all vitamers to phosphorylated forms (100). The pyridoxamine- and pyridoxine 5'-phosphates are also rapidly oxidized to PLP, although this enzyme is highly sensitive to product inhibition and any excess PLP probably limits the flux through this step (92, 102, 167). Hepatic PLP in excess of cellular binding proteins is either dephosphorylated (78) or released from the cell (83). It is frequently argued that the apparently high activities of alkaline phosphatase cause PLP that is not protein bound to be dephosphorylated; however, these estimates are made using the activity of this enzyme at its "unphysiological" pH optimum. Near neutral pH, the kinase and phosphatase activities are comparable (100). Pyridoxal oxidase activities are also fairly high, and this suggests that a substantial portion of pyridoxal will be converted to pyridoxic acid (100).

In support of this interpretation of the relative enzymatic activities in human liver, Wozenski et al (174) found that when pyridoxine and pyridoxal were given to volunteers, pyridoxal was much more rapidly converted to pyridoxic acid. In another vein, Solomon (150) noted that pyridoxamine was more effective than pyridoxal in activating erythrocyte aspartate aminotransferase, apparently because the aldehydic compound was bound to hemoglobin instead of converted to PLP.

Pharmacokinetics of B_6 Uptake and Clearance

Coburn et al (18) recently discussed vitamin B_6 kinetics. On a more molecular level, the major factor that determines plasma PLP appears to be its formation by liver (83) versus its dephosphorylation by alkaline phosphatase. This was first suggested by experiments with rat hepatocytes (78). Whyte et al (170) subsequently reported that the tissue-nonspecific (bone/liver/kidney) isozyme

of alkaline phosphatase is a major factor in determining the levels of plasma PLP. Numerous workers have noted a correlation between the low plasma PLP in liver disease and elevated plasma and hepatic alkaline phosphatase (see below). Additional evidence for hepatic degradation in humans is the observation (53) that patients with liver disease with the best hepatic blood flow exhibit the lowest plasma PLP. Identification of the primary site of PLP hydrolysis is required for an understanding of plasma PLP levels and regulation, the biochemical basis for metabolic defects in the handling of this micronutrient, and (in conjunction with clearance data) to provide an index of vitamin B_6 status.

DEFECTS IN VITAMIN B_6 ABSORPTION

Celiac Disease

In acute celiac disease there is a slower rate of appearance of PLP in blood, and the site of absorption appears shifted from the upper jejunum to more distal parts of the intestine (126). Depression is sometimes a symptom in adult celiac disease, and Hallert et al (49) found that patients' scores on the Minnesota Multiphasic Personality Inventory were brought more toward normal upon administration of 80 mg/day of pyridoxine for 6 months.

ABERRANT HEPATIC METABOLISM OF VITAMIN B_6

Hepatic and Biliary Diseases

Although defects in vitamin B_6 metabolism have been most extensively studied in cirrhosis (see below), patients with hepatitis and extrahepatic biliary obstruction also exhibit low fasting PLP and similar plasma concentration/time profiles for PLP after injection of pyridoxine (111). In all patients with liver disease, clearance of plasma PLP was more rapid than for normal controls, suggestive of a common metabolic defect. Plasma PLP is also lower in hepatocellular carcinoma (175). The one setting in which elevated plasma PLP levels have been documented is in fulminant hepatic failure (134). It was postulated that this occurred parallel to major hepatocyte destruction.

Cirrhosis

Patients with cirrhosis frequently have low plasma PLP levels even when provided a normal diet (8, 53). Ethanol probably does not inhibit intestinal uptake of pyridoxine (106). Hepatic PLP level is also lower, as is the activity of liver aminotransferases (26). This is apparently not due to a defect in PLP synthesis because cirrhotic liver has the same levels of the biosynthetic enzymes (99) and pyridoxine supplements are rapidly metabolized to pyridoxic acid (53, 111), which proceeds via PLP.

Instead, the low plasma PLP is probably due to increased degradation. Mitchell et al (111) found that PLP administered intravenously is cleared more rapidly by patients with liver disease than by controls. This is associated with elevated alkaline phosphatase in plasma (2); however, it is not clear that plasma alkaline phosphatase is directly responsible for the lower plasma PLP. Albumin-bound PLP is poorly hydrolyzed by alkaline phosphatase (82, 85), and there does not appear to be a significant difference in protein binding of PLP in patients with liver disease (111) unless alcohol consumption yields enough acetaldehyde to compete for PLP binding by proteins (82). A likely site of PLP degradation is in liver, which has been shown to have substantial phosphatase activities (100) that are elevated in cirrhosis (99). Interestingly, Shane (143) found that rats receiving approximately 30% of their caloric intake as ethanol metabolized pyridoxine relatively normally and tissue stores were not decreased. There was, however, an increase in hepatic pyridoxamine 5'-phosphate.

Attempts to normalize plasma PLP in cirrhotics have frequently had limited success. Response rates as low as 30% have been reported to intravenous pyridoxine supplementation (67), while others (53) have shown a significant plasma increment in all patients following oral pyridoxine; also, erythrocyte PLP was returned to normal by administering to patients 50 mg of pyridoxine hydrochloride per day (88).

The clinical significance of low plasma PLP is unknown. These patients do not exhibit typical symptoms of a dietary deficiency, and hence low PLP has not been considered significant. Nonetheless, many biochemical abnormalities found in vitamin B_6 deficiencies, such as elevated cystathionine (54, 118a) and decreased plasma clearance of serine, threonine, and other amino acids (121; M. Miller et al, unpublished data), are present in liver disease.

Reye's Syndrome

Using a radioenzymatic method, Faraj et al (36) reported that plasma PLP is significantly higher in Reye's syndrome (37.5 ± 6.1 μg/liter) than in controls (8.4 ± 1.5 μg/liter) or patients after treatment (8.5 ± 2.9 μg/liter).

FACTORS AFFECTING PYRIDOXAL 5'-PHOSPHATE CLEARANCE

Hypophosphatasia

Various studies have identified alkaline phosphatase as the major enzyme responsible for PLP hydrolysis by rat (81) and human (100) liver, and implicated this enzyme as a major determinant of plasma levels of this coenzyme (2, 67, 82, 99). However, the most conclusive evidence for the control of plasma PLP by this enzyme was recently reported by Whyte et al (170) in studies of patients with hypophosphatasia, an inborn error usually

transmitted as an autosomal recessive trait. This condition is characterized by rickets and osteomalacia, low serum alkaline phosphatase (the nonspecific, bone/liver/kidney isozyme) and increased pyrophosphate and phosphoethanolamine in urine and plasma. In 14 patients representing all clinical forms of hypophosphatasia, plasma PLP was 1174 nM (range 214–3839 nM) compared to 57 ± 26 nM in control subjects (170). Plasma levels of other forms of vitamin B_6 and urinary pyridoxic acid appeared normal in the subset of patients examined. The authors noted that neither the clinical hallmarks of vitamin B_6 deficiency nor the neurotoxicity found with megadoses of pyridoxine are associated with hypophosphatasia.

Renal Disease

Plasma PLP is abnormally low in many patients with chronic renal failure and those undergoing maintenance hemodialysis, intermittent peritoneal dialysis, or kidney transplant with or without normal or nearly normal kidney function (46, 60, 62, 69, 70, 158). Spannuth et al (153) concluded that this was due to an increased metabolic clearance of PLP, which is supported by the absence of PLP in dialysis fluid (69). Heaf (52) did not find differences in plasma pyridoxine using a microbiological assay with *Saccharomyces carlsbergensis* as the test organism.

The low plasma PLP in these conditions is often associated with increases in the ratio of apo- to holo-forms of erythrocyte transaminases and many of the patients exhibit clinical signs similar to those in vitamin B_6 deficiency (158). Plasma low-density lipoproteins are also lower and some abnormalities in plasma amino acids have been attributed to vitamin B_6 deficiency (60).

Kopple et al (62) investigated the daily pyridoxine supplement necessary to normalize vitamin B_6 status in chronic renal failure as assessed by the erythrocyte glutamate-pyruvate transaminase (EGPT) activities and stimulation by added PLP (EGPT index). Daily administration of 5.0 mg of pyridoxine hydrochloride normalized the EGPT index for most patients undergoing maintenance dialysis (a dose of 10 or 50 mg/day was uniformly effective). Patients undergoing peritoneal dialysis and undialyzed patients with renal failure were rapidly normalized by 2.5 mg/day, and 5 mg/day was recommended. Somewhat higher levels may be safer when the patients are taking vitamin B_6 antagonists or have sepsis. Studies by Lacour et al (69) confirmed these observations and included kidney transplant patients in the group requiring supplemental pyridoxine. They further stressed that the higher therapeutic doses of pyridoxine widely used in hemodialysis patients produce a supraphysiological increase in plasma PLP.

The stimulation in vitro of alanine aminotransferase activity by PLP in patients with a renal allograft differed for patients given cyclosporin A versus azathioprine. Since plasma PLP was abnormally low in both groups (46),

azathioprine itself (or metabolites) may cause the very high stimulation of alanine aminotransferase. Watts et al (168) have observed that pyridoxine supplementation is also useful in one third to one half of the patients with type I primary hyperoxaluria (hyperoxaluria with hyperglycollic aciduria) or the less common type II primary hyperoxaluria (hyperoxaluria with L-glyceric aciduria). Otherwise, the prognosis is bad with respect to recurrent urolithiasis, calcium oxalate nephrocalcinosis, renal failure, and complications of systemic oxalosis, and the success of renal transplantation is lower. It appears that the patients that respond to pyridoxine have a reduction in oxalate biosynthesis, perhaps because of activation of a PLP-dependent transaminase responsible for other reactions relating to oxalate.

CONDITIONS ASSOCIATED WITH LOW PYRIDOXAL 5'-PHOSPHATE

Pregnancy, Lactation, and Oral Contraceptives

The blood levels of PLP are lower in pregnant women (and high in fetal cord blood), which may indicate a relative deficiency in pregnant women (22, 33, 74). Contractor & Shane (22) found that blood PLP increases normally in response to a pyridoxine load; hence, vitamin B_6 metabolism does not appear to be impaired in pregnancy. The fetus utilizes a significant amount of maternal PLP, but this alone cannot account for all of the increased maternal vitamin B_6 requirement (144). Toxemia can further increase maternal requirements for pyridoxine (144). Temesvari et al (162) found that 100 mg of pyridoxine given to pregnant women at term decreased maternal and newborns' cord blood oxygen affinity (i.e. increased P50).

Estrogen oral contraceptives have also been suggested to cause depletion of vitamin B_6 based on the tryptophan load test and plasma PLP (30, 110, 130, 131). In other studies, neither plasma PLP nor urinary pyridoxic acid were found to be abnormal (10, 75), and estrogens had no effect on methionine metabolism (75). Instead, it appears that estrogens directly affect tryptophan metabolism (7). Another complication in tryptophan load experiments might be that several tryptophan metabolites inhibit pyridoxal kinase and activate pyridoxine 5'-phosphate oxidase (161). Miller (108) recommends monitoring the vitamin B_6 status of women using these drugs.

High concentrations of pyridoxine have been reported to be antilactogenic and hypolactinemic; however, the lower levels found in prenatal and typical multivitamin supplements elevate plasma and milk PLP without reducing prolactin or lactation (4).

There has been considerable controversy over the value of pyridoxine in premenstrual syndrome. Few controlled trials have yielded significant effects (47); however, Williams et al (172) reported that in 434 of 617 patients

examined, an improvement was found in 7 of 9 symptoms assessed upon pyridoxine therapy.

Hematologic Disorders

There is extensive literature regarding the "pyridoxine-responsive" anemias. It is recommended that pyridoxine therapy (i.e. 50–200 mg of pyridoxine per day) be tried in patients with sideroblastic anemia, although an "optimal response" is obtained in fewer than half of the cases (173). One explanation for the response to pyridoxine is that the patient has a defect in delta-aminolevulinate (ALA) synthetase that results in a low affinity for PLP and thus in a decreased activity and/or increased degradation of this enzyme. For example, ALA synthetase activity was low in a patient with primary acquired sideroblastic anemia with or without supplementation of the in vitro assay with PLP (98). Upon treatment of the patient with 600 mg of pyridoxine per day for several months, the activity was restored to normal when assayed with PLP, and to 50% of normal without PLP addition. A lower availability of PLP may also be important in both hereditary and acquired sideroblastic anemias (173).

There appears to be a vitamin B_6 deficiency in sickle cell anemia (118). However, pyridoxine therapy has been reported to be rarely effective in other myelodysplastic syndromes (11a).

The metabolism of vitamin B_6 by red blood cells has been characterized for normal individuals (150, 151) and in anemic and alcoholic subjects (152). Both of these abnormal conditions are frequently accompanied by high pyridoxal kinase activities. Racial differences in pyridoxal kinase activity have been noted (15a,b, 151). The activity in red blood cells from black people is approximately 50% lower than of North American whites; this has been shown to be polymorphic and is due to a higher gene frequency among blacks for the allele responsible for the enzyme deficiency. Abnormal red cell metabolism of vitamin B_6 has also been observed in β-thalassemia (3).

Atherosclerosis

The first association of vitamin B_6 and vascular disease was the observation by Rinehart & Greenberg (128) that monkeys fed a diet deficient in this nutrient developed atherosclerosis. There have been relatively few studies (63, 171) of the human implications of this finding; however, PLP levels are markedly lower in coronary patients (43) and in patients suffering from myocardial infarction compared to a healthy control group (142). It has been suggested (142) that PLP levels may be a far more sensitive indicator of the risk of myocardial infarction than plasma cholesterol or HDL.

This correlation may reflect low plasma levels of PLP as a consequence of myocardial infarction or may indicate that vitamin B_6 status is related,

perhaps causally, to the development of atherosclerosis. Although the former has not been ruled out, there are several reasonable mechanisms whereby deficiencies in PLP could contribute to the progression of this disease. These are briefly reviewed below.

SULFUR AMINO ACID METABOLISM Vitamin B_6 is known to be intimately involved in sulfur amino acid metabolism (159). McCully (94) first noted that patients with homocysteinemia show a high incidence of atherosclerosis at a very early age. Homocysteine is an intermediate in the metabolism of methionine and accumulates in vitamin B_6 deficiencies or when there is an inborn error in this pathway. Homocysteine has been shown to promote vascular injury and thrombosis in experimental animals (50); it also promotes cellular growth (17).

Several groups have proposed that the presence of homocysteine in plasma at elevated levels due to marginal vitamin B_6 deficiences could be a major contributing factor in atherosclerosis (e.g. 95, 160). Homocysteine is often difficult to measure in plasma because it exists as mixed disulphides (42). Smolin and Benevenga (146, 147) have studied the effects of both vitamin B_6 deficiency and associated decreases in food intake on plasma homocysteine and atherosclerosis.

Miller et al (109) have reported that the level of dietary protein influences the concentrations of plasma and urinary B_6 compounds. This could mean that high-protein diets exacerbate any limitation in PLP availability for reactions that are involved in the development of atherosclerosis, such as the formation of homocysteine.

LYSYL OXIDASE Lysyl oxidase is an extracellular enzyme responsible for elastin and collagen cross-linking. It requires PLP for activity (116) and is profoundly affected by vitamin B_6 deficiency (115). It has been proposed that this may account for the arterial wall abnormalities seen in vitamin B_6–deficient chickens.

CHOLESTEROL METABOLISM Vitamin B_6 deficiency has been reported to increase the incorporation of labeled acetate into cholesterol by rats (86) and to decrease basal synthesis rate of primary bile acids and the incorporation of lipoprotein cholesterol into biliary sterols in monkeys (156). Abnormalities in both vitamin B_6 and cholesterol are associated with various diseases. For example, patients with chronic glomerulonephritides with and without nephrotic syndrome have significantly lower levels of plasma PLP ($P < 0.001$) and higher levels of serum cholesterol ($P < 0.001$) (68). The mechanism for this link between PLP and cholesterol metabolism is not known. It may simply reflect the inability of cells to take up lipoproteins when vitamin

B_6 is limiting. The decreased bile acid synthesis might be due to altered amino acid and/or taurine metabolism (both of which involve multiple enzymes dependent on PLP). Vitamin B_6 is also known to be involved in the metabolism of unsaturated fatty acids (114). A more recently considered hypothesis is that there is a link between cholesterol metabolism and the handling of another lipid class, namely sphingomyelin (103, 157).

PLATELET AGGREGATION Since PLP inhibits in vitro platelet aggregation, it has been suggested that it might be a useful antithrombotic agent. However, Schoene et al (138) were unable to observe any effect of 100 mg pyridoxine/day on in vitro platelet aggregation in a randomized, double-blind study with healthy adult males.

Neurological Disorders

Defects in vitamin B_6 metabolism may contribute to some types of neurological abnormalities (19, 87, 89, 93, 119, 123, for examples), because of the involvement of PLP in numerous key pathways of neural function (namely neurotransmitter synthesis, amino acid metabolism, sphingolipid biosynthesis, and degradation) (24). Vitamin B_6 deficiencies have multiple neurological effects (16, 24); however, a cause-and-effect link between defective vitamin B_6 metabolism and neurological disorders has not been proven.

Urinary excretion of pyridoxic acid and tryptophan metabolites in patients with Down's syndrome is suggestive of abnormal vitamin B_6 metabolism (93). Furthermore, the concentrations of PLP in platelets from subjects with Down's syndrome is significantly lower than for normal controls (93). Pyridoxine supplements increase serum PLP, but result in no improvement in the scores of Down's patients on the Stanford-Binet test (19). Coleman et al (20) did not find significant differences in mental age, cranial circumference, or tongue protrusion in a double-blind study of the clinical effects of pharmacological doses of vitamin B_6 in Down's syndrome. A side effect of long-term administration of pyridoxine to these children was blistering of the face and hands in areas where the skin was exposed to the sun. Differences in cortical auditory evoked potentials were found in the B_6-treated group at three years of age (39).

Ebadi et al (31) reported that PLP concentrations and pyridoxal kinase activities were similar in whole brains from normal and epilepsy-prone rats; however, significant differences were observed in specific brain regions (e.g. cerebellum and cortex). The authors caution against interpreting this as abnormal vitamin B_6 status until the functional significance can be determined.

Neurotoxicity results from consumption of pyridoxine much above the Recommended Dietary Allowance (122, 137). Little is known about the cause

of neural damage, although it has been characterized in detail with animal models. In rats, extremely large amounts of pyridoxine cause damage to, and loss of, large primary sensory neurons (65). In view of the lack of information concerning the biochemical mechanism behind this disorder, it is interesting that Snell hypothesized in 1964 (148) that there might be conditions in which pyridoxine could result in adverse effects if it was allowed to accumulate as the 5'-phosphate in tissues, since this form acts as an inhibitor of many PLP-dependent enzymes. It is also noteworthy that very high levels of PLP per se, as in hypophosphatasia, have not been associated with neurological symptoms (170). Kroll (66) recently noted a case in which administration of pyridoxine for neonatal seizures resulted in acute hypotonia requiring assisted ventilation. He cites other examples of this phenomenon and speculates that it may be due to a burst of neurotransmitter synthesis from accumulated precursors.

Collagen Disorders

Both riboflavin and vitamin B_6 deficiencies are associated with impaired collagen maturation (125) and elastin cross-linking (117); carbonyl reagents that are known to impair PLP function, such as isoniazid, also alter the water solubility of collagen (14). As already cited, this may be caused by a decreased activity of lysyl oxidase, which is profoundly affected by vitamin B_6 deficiency (115).

Cancer

Cancer patients frequently exhibit signs of unusual metabolism of vitamin B_6, such as lower plasma PLP despite normal urinary pyridoxic acid. This has been reported in patients with breast cancer (124) and Hodgkin's disease (15). Tryptophan metabolism is also abnormal in Hodgkin's disease (15), hemoblastosis (23), and breast (132) and bladder cancer (9).

Thanassi and coworkers (120, 163, 164) have established that pyridoxine (pyridoxamine) 5'-phosphate oxidase is low or absent from hepatomas, which implies that these cells must obtain PLP from circulation. Hepatocarcinogens decrease the levels of enzymes involved in PLP synthesis without altering the activity of the phosphatase (59). There is also some evidence that tumors may form a novel metabolite of pyridoxine (165).

Studies with experimental animals have found that the growth of some types of tumors is inhibited by diets deficient in pyridoxine (61, 104, 107, 166). Vitamin B_6 deficiencies affect host susceptibility to Maloney sarcoma virus-induced tumor growth in mice (44). The growth of spontaneous mammary tumors in strain C3H mice was unaffected by pyridoxine deficiency (112).

DiSorbo et al (27) reported that pyridoxine at millimolar concentrations is toxic to hepatoma cells in culture, and pyridoxal inhibited the growth of B16 melanoma cells in culture and after establishment in mice (28).

The importance of these observations to human cancer incidence or progression is not clear, however. Ladner & Salkeld (72) observed that cancer patients undergoing radiation therapy for gynecological carcinoma have an apparent decrease in plasma B_6. They also noted that the 5-year survival rate of patients with stage II endometrial carcinoma was increased by administration of pyridoxine. Bell (6) reported that women who excrete less pyridoxic acid than average have a higher probability of recurrence of breast cancer than those with more normal excretion. Gailani et al (40) did not observe an effect of treating patients with a pyridoxine-deficient diet for 10 to 80 days, nor of administering a pyridoxine antagonist, 4-deoxypyridoxine. Ladner & Salkeld (72) have claimed, however, that correction of vitamin B_6 deficiency increases the survival of patients with cervical and uterine carcinoma. A prospective trial with 121 patients compared the effects of administering a placebo, pyridoxine, or topical thiotepa on the recurrence of stage 1 bladder cancer (12). Although the outcome was similar when the groups were compared as a whole, the differences were significant when patients having recurrences within the first ten months or followed up in less than ten months were excluded.

Inborn Errors

While a number of pyridoxine-responsive disorders are attributable to inborn errors of PLP binding by apo-proteins (38, 133), few cases indicating a defect in overall vitamin B_6 absorption or metabolism have been described (140, 170). In addition, all disorders of similar nature may not be pyridoxine responsive, as exemplified by homocystinuria (due to diminished activity of cystathionine β-synthase) in which only about half of the patients responded to pyridoxine therapy (113).

Drug–Vitamin B_6 Interactions

Various agents complex with the free aldehyde of pyridoxal and PLP and result in vitamin B_6 deficiency (129, 136). Carbonyl reagents (e.g. hydrazine, INH, penicillamine) are widely thought to act by competitively displacing PLP from the binding sites of apo-enzymes; however, McCormick et al (91) demonstrated that in some instances they form a complex with pyridoxal that is inhibitory for pyridoxal kinase. Co-administration of pyridoxine is often helpful in minimizing side effects of such agents (141). Pyridoxal 5'-phosphate has also been used to protect against the toxicity of certain chemicals—in particular, acetaldehyde (57).

Other Conditions

Vitamin B_6 deficiency is accompanied by impaired humoral and cell-mediated immunity, reduced delayed hypersensitivity responses, prolonged survival of skin allografts, depletion of thoracic duct lymphocytes and reduced lymphocyte proliferation, impaired thymic epithelial cell function, and maintenance of normal T-cell function in vivo (45). Phototherapy for hyperbilirubinemia in infants results in an apparent decrease in plasma PLP, as reflected in the activity coefficients of erythrocyte and plasma transaminases (135). This was attributed to the light sensitivity of vitamin B_6. Haller et al (48) found that muscle B_6 of patients with McArdle's syndrome was approximately one fifth of control values, but they concluded that this was due to a decrease in phosphorylase and not vitamin B_6 status. Large amounts of caramel color produced by the ammonia process have been associated with hematologic toxicity in rats. Spector & Huntoon (154) found that these compounds are inhibitors of pyridoxal kinase and thereby inhibit the accumulation of pyridoxine by brain slices.

Folkers and coworkers have advocated the use of pyridoxine in carpal tunnel syndrome with testing of patients for biochemical signs of vitamin B_6 deficiency as a criteria for nutritional therapy (34, 35). Not all investigators have noted a similar response (1, 145), which Byers et al (13) have suggested may be a result of an unrecognized peripheral neuropathy that complicates the symptomatology. Care must be taken because at least one example of neuropathy due to ingestion of excessive amounts of pyridoxine for carpal tunnel syndrome has been reported (37).

SUMMARY

It is clear that many diseases are known to involve defects in vitamin B_6 metabolism, but that even more await definitive studies. Furthermore, some functions of vitamin B_6, such as its role in glucocorticoid action (21), have been discovered so recently that the medical implications have not yet been fully explored.

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