VITAMIN B6

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Vitmain B_6 is essential for many metabolic pathways involving protein and its constituent amino acids. Consequently, vitamin B_6 status in each of us is important in health effects all the way from our childhood physical growth to our lifelong health and mental acuity.

Food contains three natural forms of vitamin B_6: pyridoxine, pyridoxamine, and pyridoxal. Pyrodoxal, with phosphate added to its molecule, is the form of vitamin B_6 that is used by our bodies as a coenzyme. The commercial vitamin form, pyridoxine hydrochloride, has the hydrochloride added for stability and increased shelf life. That form is artificial but is well utilized by most individuals. However, the body cannot use pyridoxine directly. Two metabolic steps are needed.

First, the pyridoxine must be phosphorylated, that is, phosphate is added to the ring-structure of the molecule. Pyridoxine, pyridoxal, and pyridoxamine are all well-absorbed through the mucosa of the small intestine. Inside cells, all these forms are phosphorylated using the enzyme pyridoxal kinase. Generally accepted wisdom is that magnesium is needed to activate kinase enzymes-enzymes that phosphorylate. However, there is published experimental work, showing in vitro, that this particular phosphorylating enzyme in human brain tissue has higher affinity for zinc and higher activity with zinc than with magnesium. This was published by McCormick and others in the *Journal of Biological Chemistry*, volume 236, in 1961. In spite of this finding, many experts still credit magnesium with activating this and all kinase enzymes. The phosphate, by the way, comes from adenosine triphosphate or "ATP," which is a principal molecule for supplying energy in our bodies.

After phosphorylation, if the cell started with pyridoxal, the biochemistry is completed. The pyridoxal 5-phosphate coenzyme or P 5-P is ready to go to work. All it has to do is link up with its apoenzyme to form the complete or holoenzyme. The reference text, *Methods in Enzymology*, volume 18A, discusses phosphorylation of B_6 forms on page 618. The statement is made that the phosphorylating kinase prefers pyridoxal over pyridoxine. That is, the enzyme phosphorylates pyridoxal faster than it phosphorylates pyridoxine. With pyridoxine, the vegetable source form of B_6, this phosphorylation produces pyridoxine phosphate. Then next, the pyridoxine phosphate has to be oxidized by an oxidase enzyme that is assisted by vitamin B_2, riboflavin, as flavin

mononucleotide, "FMN." Here's one of the rubs in supplementing with pyridoxine. If vitamin B_2 is low as FMN, then the rate of P 5-P production is typically decreased by 60%.

To summarize the chemistry, which I hope isn't too complicated, pyridoxine has to go through two steps to form P 5-P. In the first step, it is phosphorylated, and remember, pyridoxine is not the preferred form for the kinase. Pyridoxal is preferred. And in the second step, pyridoxine phosphate needs vitamin B_2 as FMN to efficiently form pyridoxal phosphate.

Now, what happens if we start out with P 5-P in the first place? Well, it can be absorbed intact, or in pyridoxal form without the phosphate. Pyridoxine and pyridoxal are known to be synergistic in uptake with magnesium. On the cellular basis, Abraham and others did a clinical measurement of this in premenopausal women and found that oral B_6 at 100 milligrams twice per day very significantly raised red blood cell (RBC) magnesium levels after four weeks of supplementation. Their work is published in *Annals of Clinical and Laboratory Science*, volume 11(4), 1981, starting on page 333. Growth effects and synergism between magnesium and vitamin B_6 have also been studied in animals. A study by Kubena and others in the *Journal of the American College of Nutrition*, volume1(4), 1988 came to a similar conclusion-deficiencies of pyridoxine and magnesium impair growth and physiological functions in a multiplicative or synergistic fashion.

I've heard criticisms that pyridoxal 5-phosphate is destroyed in the stomach or in the gut. These criticisms have come, without documentation, from pyridoxine fans. Actually, it's likely that some of the phosphate is knocked off. That's alkaline phosphatase's job--to rearrange the phosphate supply. But who cares? We've still got the pyridoxal--stomach won't make pyridoxine from pyridoxal. And once absorbed, the pyridoxal is more readily phosphorylated-according to the very authoritative enzymology reference cited earlier. And, the pyridoxal doesn't need FMN and another enzyme to reach the coenzyme form.

At the Klaire Laboratories International Symposium in Athens, Greece, in 1995, Dr. Emar Vogelaar reported on blood analyses of human subjects taking pyridoxal 5-phosphate. He found a better than 15% average increase in blood pyridoxal after two weeks of supplementation with 50 milligrams per day. So, there's no question about bioavailability-it gets in.

Finally, there's the problem of interfering vitamers in pyridoxine (substances that are similar to pyridoxine). At doses above 500 milligrams per day, peripheral or sensory neuropathy can occur in some individuals. This was widely reported over 10 years ago. Pyridoxine took the blame, but less publicized research later focussed the blame on vitamer impurities in the pyridoxine. Nothing is 100% pure, and pyridoxine is no exception: 4-deoxypyridoxine and methoxy-pyridoxine are known pyridoxine antagonists. However, when pyridoxine is carefully

processed through several refinements to form pyridoxal 5-phosphate, the concentration of interfering vitamers drops substantially. Also, less P 5-P is needed than pyridoxine. No controlled studies have given exact comparisons, but I've found 50 milligrams per day of P 5-P to do the work of 200 to 500 milligrams of pyridoxine hydrochloride. Also, some case histories are worthwhile here. Several individuals presenting sensory neuropathy following high doses of pyridoxine had their conditions completely relieved by discontinuing the pyridoxine, taking no B_6 in any form for 3 days, then taking 50 milligrams per day P 5-P for five days with no further symptoms.

To summarize, pyridoxal 5-phosphate has the advantages over pyrodoxine hydrochloride of:

- Being the actual coenzyme form.
- Avoiding the need of oxidation to pyridoxal, which requires FMN, which in turn has to be formed from vitamin B_2 (riboflavin), which itself has to be phosphorylated-something that occurs in the intestinal mucosa and depends on proper mucosal function. And this phosphorylation of riboflavin is magnesium dependent.
- Pyridoxal phosphate may avoid phosphorylation, which may be zinc-dependent or magnesium-dependent in humans and could be a weak step if there is zinc or magnesium insufficiency.
- The P 5-P form is purer, and less is needed to achieve the same cofactor effects.
- To my knowledge no sensory neuropathy has ever been reported with use of P 5-P.

So, P 5-P has the edge over pyridoxine in magnesium deficiency, in zinc deficiency, in purity, and in potency.

Now, what does coenzyme P 5-P do?

In body tissues it is necessary for amino group transfer called transamination. This process balances the quantities of amino and organic acids. The balance between alanine and pyruvate or aspartic acid and oxaloacetic acid are examples. P 5-P also is the coenzyme for decarboxylation. That is, taking the carboxyl group-the COOH or organic acid group-away from amino acids. Formation of histamine from histidine is an example of this. Finally, pyridoxal phosphate is a necessary coenzyme for certain molecular marriages or breakups where two amino acids join or where some are split into two parts. Marrying homocysteine and serine to form cystathionine is an example. Then, splitting the

cystathionine into cysteine and alpha-ketobutyric acid is an example of its divorce function. Both of these steps, by the way, are documented metabolic error points in humans. Homocystinuria, of mild degree, is a relatively common occurrence, with a frequency of about 1 in 100. Cystathioninuria is much rarer. Both conditions were early examples of medical use of a vitamin to potentiate the activity of a genetically weak enzyme.

So, the basic clinical use of pyridoxal 5-phosphate is to potentiate activity of P 5-P dependent enzymes. There are dozens and dozens of these enzymes in human metabolism. An amino acid analysis performed on blood or urine at a clinical laboratory often shows presumptive evidence of P 5-P need. Elevations of alanine, aspartate, glycine, serine, tyrosine, valine, leucine, isoleucine, homocysteine, cystathionine, alpha-aminoadipic acid, or beta-alanine, just to name a dozen B6 sensitive amino acids, can signal increased need for coenzyme P 5-P.

Also notable are the clinical findings of increased cellular magnesium when vitamin B6 is administered. Individuals with poor magnesium retention may need B6. Another finding is reduced edema and swelling when B6 is taken. An early study in 1954 by Gugginheim published in *Endocrinology*, volume 54, showed that B6 deficiency can lead to delayed water excretion. Humans that experience abdominal bloating or swollen ankles may need B6 and may also need increased protein in their diets as well as more exercise.

Doctors Karl Folkers and John Ellis have long ago published their clinical findings on the benefits of vitamin B6 in carpal tunnel syndrome. This syndrome features morning stiffness in the fingers, impaired finger sensations, weakness of hand grip, and edema in the hands. Elsewhere in the body there is a frequent occurrence of rheumatism, bursitis, and edema. Karl Folkers was Director of the Institute for Biomedical Research at the University of Texas. In 1986, he gave the Priestly Medal Address on B6 and carpal tunnel syndrome to the American Chemical Society. His lecture is recorded in the April 21st, 1986 issue of *Chemical and Engineering News*. Dr. Folkers did double blind studies with a control group that showed successful therapy using B6. He measured its effect as P 5-P on a transaminase enzyme. Doctor John Ellis has reported his findings of beneficial vitamin B6 effects in carpal tunnel syndrome, childhood diabetes, tendonitis, edema, and arteriosclerosis. This is in his own publication: "Meditations on Vitamin B_6," dated 1989. The arteriosclerosis finding, no doubt, is related to the now infamous condition of homocystinuria and occlusive arterial disease. This is alleviated with vitamin B_6 and often folate and B_{12} as well. In the last seven or eight years articles on B_6, homocystine and cardiovascular disease have been published in the *New England Journal of Medicine* and in the *Journal of the American Medical Association* several times. and also in *NOHA NEWS*, Winter, 1998.

Finally, Dr. Bernard Rimland and others have published on the benefits of vitamin B_6 and magnesium in autism and in developmental disorders in children. In autism, parents have monitored functional improvement or regression with use of megadose pyridoxine-usually 250 to 500 milligrams per day. By this measure, the ratio of improved autistics to worsened autistics is about 10 to 1. No laboratory test is needed, in my opinion, for trial use of pyridoxine or pyridoxal in autism or developmental problems. Occasionally, some autistics eventually cease to benefit from 500 milligrams per day of pyridoxine and a few worsened initially. Many of those individuals improved after switching to pyridoxal 5-phosphate as reported to me by Dr. Rimland.

In conclusion, pyridoxal 5-phosphate has specific metabolic applications determined by amino acid analysis and other medical tests. Additionally, published studies show benefits in conditions of edema and water retention, magnesium deficiency, peripheral neuropathy, carpal tunnel syndrome, tendonitis, rheumatism, cardiovascular occlusions and myocardial infarcts, learning and developmental disorders, and autism.

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