



Vitamin B₆ Antagonists

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VITAMIN B₆ is a catalyst of considerable biological importance. Studies during the past 15 years have established a key role for this vitamin in protein and amino acid metabolism and, somewhat less firmly, in fat metabolism. It would seem, therefore, that suitable antagonists to this vitamin might be of therapeutic importance. We are actually in a most curious situation with respect to vitamin B₆ and its antagonists—so that I trust the present discussion is not a mere repetition, for yet another vitamin, of further examples of chemical alteration of the vitamin molecule providing substances antagonistic to the vitamin, some of which may possess clinical value. To possess therapeutic significance, such antagonists must have properties other than mere antagonism.

The properties of the vitamin B₆ group and the nature of the antagonists have been recently and adequately reviewed.^{1,2,3,4} I shall, therefore, concentrate my attention upon some newer aspects of the problem of vitamin B₆ antagonists, particularly those having some therapeutic implications.

The field for antagonists in the vitamin B₆ group, with its many related members, would seem to be wide enough. I shall use the term vitamin B₆ to designate all active members, and the specific common names for particular members of the group. As illustrated in Figure 1, at present vitamin B₆ comprises pyridoxine, pyridoxamine, pyridoxal and their respective phosphates. There doubtless exist in nature and certainly have been prepared in the laboratory several substances which, upon breakdown, yield vitamin B₆, as, for example, the pyridoxylidene amines, the pyridoxyl amines,⁵ and the pyridoxylamino acids.^{6,7}

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THE ACTIVE FORM

It appears that vitamin B₆ exerts its action by being converted into pyridoxal-5-phosphate, which is the prosthetic group of a variety of catalytic proteins. Pyridoxal-5-phosphate is known to be the coenzyme of the amino acid decarboxylases, of transaminases, and is associated with enzymes concerned with the breakdown of tryptophan, and its synthesis, the breakdown of serine, threonine, cysteine, the cleavage of thioethers, and several related reactions.² In all of these cases pyridoxal-5-phosphate is the active coenzyme; and, with one exception, pyridoxamine phosphate and pyridoxine phosphate are not active, nor are the unphosphorylated bases. This exception is found in the activity of pyridoxamine phosphate in transaminase.^{8,9} There are, in addition, transaminases which transaminate pyridoxamine, and certain purines¹⁰ and enzymes also exist which phosphorylate pyridoxal and certain other pyridoxine derivatives.¹¹ In fact, so general is the involvement of pyridoxal phosphate with the reactions of the amino acids, that today it is the first coenzyme one looks for in any reaction of amino acids, and it frequently occasions surprise when it is not the coenzyme. The requirement for vitamin B₆ in the rat is dependent upon the protein intake, and under circumstances of vitamin B₆ deficiency various aspects of protein synthesis and degradation are impaired.^{1,2,4} Somewhat less precise, but nonetheless real, is the increasing evidence, some confusing, all very general, of the relationships between vitamin B₆ and fatty acid requirements.

There are, of course, many alterations possible in the molecules of vitamin B₆, but since pyridoxal-5-phosphate is the active form it is evident that if unreactive groups are placed at position 4 or 5 the substance cannot act

as the vitamin, and may possibly be an antagonist. By placing a methyl at position 4 one has what is usually called desoxypyridoxine. While modern terminology would call this desoxypyridoxine, we will retain the term desoxypyridoxine. Another desoxypyridox-

chemically, but I do not happen to know of any direct conversion by biological systems. While many alterations in the molecule of vitamin B₆ can be made, the compounds resulting from such alterations are relatively inert, except for those illustrated in the figure.

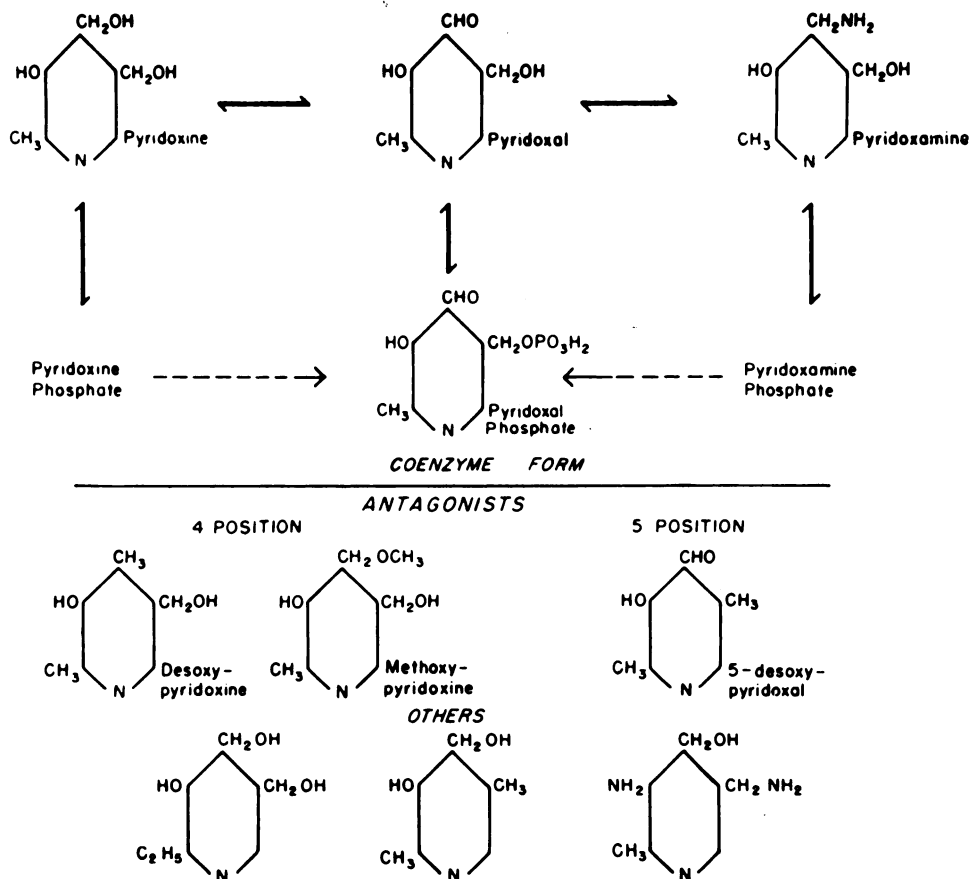


Fig. 1. Relationship of the members of the vitamin B₆ group and their antagonists.

ine is obtained by placing a methyl at position 5, frequently called 5-desoxypyridoxal. There is another antagonist in which the 4 position has been replaced by a methoxy methyl, usually called methoxypyridoxine. These relationships are illustrated in Figure 1.

Pyridoxine, pyridoxal, and pyridoxamine are interconvertible, and by way of a reaction with ATP are converted into their respective phosphates. It may have been demonstrated somewhere that the phosphates are interconvertible *per se* by biological systems. Certainly the phosphates are interconvertible

Of these, three have been given trivial names: desoxypyridoxine, methoxypyridoxine, and 5-desoxypyridoxal. These and others interfere with the utilization of vitamin B₆ in one or another organism. The one of greatest importance, or at least the one receiving the most adequate study, is *desoxypyridoxine*, and our attention will be concentrated on it.

DESOPYRIDOXINE

There is a wide and significant literature on the effects of vitamin B₆ deprivation upon brain excitability,^{12,13} adrenal function,¹⁴ reproduction,¹⁵ arteriosclerosis,¹⁶ hypertension,¹⁷

disorders of the skin,^{18,19} etc. In most of these, particularly in humans,²⁰⁻²⁴ the deficiency has been brought about by using not only a vitamin B₆-deficient diet, but desoxypyridoxine as well (the 4-desoxy compound is meant). These experiments generally employ the assumption that the vitamin antagonist merely accentuates the deficiency. The lesions observed are usually rapidly reversible by administration of vitamin B₆, and are prevented from developing by a normal amount of vitamin B₆. Yet there are several indications that, in reality, one is dealing, in 4-desoxypyridoxine antagonism, with phenomena not all attributable to frank vitamin B₆ deficiency.

It is in this respect that the action of desoxypyridoxine is of somewhat more interest than simple vitamin competition and offers some possibilities of therapy—the latter, so far, not too well pursued. The correspondence between the observations on straight deficiency and administration of desoxypyridoxine are not always all they should be, which led Stoerk²⁵ to describe “acute” (that produced by desoxypyridoxine) compared to “chronic” deficiency, and to point out that the following characters were associated with the acute deficiency—that is, that the following were observable when desoxypyridoxine was present, namely:

1. A dermatitis of the tail in rats.
2. A lack of response to antigen.
3. The occurrence of Tyzzer's disease in mice.
4. Regression of lymphosarcoma implants in mice.

And finally, one which perhaps because of the long list of others, seemed to have been forgotten:

5. No fall in the vitamin B₆ content of the liver (or other organs).

This is particularly important since in this case one has the symptoms of vitamin B₆ deficiency without actual tissue deficiency of the vitamin.

When a rat or mouse is placed on a vitamin B₆-deficient diet, after a period of 3 to 4 weeks it develops certain characteristic symptoms.

If the tissues from such an animal are analyzed it will be found that the total vitamin B₆ content has decreased, the pyridoxal phosphate content has decreased,^{25,26,27} and, if one measures the activity of the enzymes, transaminase in heart and liver,²⁷ or glutamic decarboxylase in brain,²⁸ these too will have decreased. If desoxypyridoxine is added to this vitamin B₆-deficient diet, the symptoms appear much sooner; superficially they seem the same and are completely alleviated by a supply of vitamin B₆. But under such “acute” deficiency, the vitamin B₆ content remains essentially the same as normal,^{25,26,27} the pyridoxal phosphate content is high,^{25,27} and the activity of transaminases of liver and heart,²⁷ and the activity of glutamic decarboxylase in the brain²⁸ remain essentially unaltered, unless the deficiency is allowed to go to really serious lengths. That desoxypyridoxine is antagonized by vitamin B₆ there is no question; but its action involves more than the antagonism of the vitamin. One might almost say that while vitamin B₆ is an antagonist for desoxypyridoxine, it looks as though desoxypyridoxine is not an antagonist for vitamin B₆. This offers some hope for a therapeutic use, and some promising attempts have been made in experimental tumors,^{25,29-36} with occasional clinical application. There are several practical difficulties, and no one is yet proposing an actual widespread clinical usefulness for this antagonist.

MODE OF ACTION

Its mode of action, so far as analyzed, seems to be the following. 4-Desoxypyridoxine does not interfere with various aspects of vitamin B₆ formation or metabolism, illustrated in Figure 2, but it is itself phosphorylated, and while the phosphate does not displace pyridoxal phosphate from the enzymes once the latter has been firmly attached, still desoxypyridoxine phosphate can compete with pyridoxal phosphate when they both have an essentially equal chance of reaching the enzyme.³⁷

In Figure 2, the site of action of desoxypyridoxine is not at *A* or *B*, but rather at *C*,

and biologically desoxypyridoxine + ATP forms desoxypyridoxine phosphate which becomes adsorbed to the enzyme and prevents pyridoxal phosphate from adsorbing, and thus activating, the enzyme. But both the phosphorylation (B) and the adsorption to the

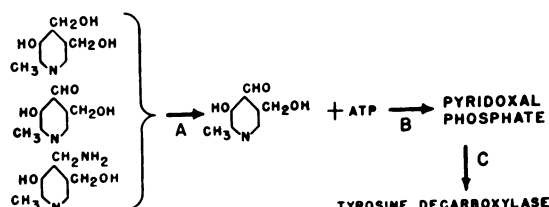


Fig. 2. Reactions involved in the activation of enzymes with members of the vitamin B₆ group.

enzyme (C) occur only when pyridoxal (for B) or pyridoxal phosphate (for C) are very low. This is probably why desoxypyridoxine is an active inhibitor essentially only at low levels of vitamin B₆. This type of study has been extended in two directions. First, the enzyme B in Figure 2 has been studied by Hurwitz.¹¹ This enzyme reacts with and phosphorylates a variety of substituted pyridines. It was shown, as illustrated in Figure 3, that 2-ethyl-3-amino-4-ethoxymethyl-5-

ation. It is perhaps surprising that pyridoxine is such an inhibitor.

Second, Meister, Sober and Peterson⁹ have employed crystalline desoxypyridoxine phosphate and pyridoxine phosphate³⁸ and have shown them to be capable of inhibiting transaminase when allowed to adsorb to the enzyme before access to pyridoxal phosphate. The binding of inhibitors to the enzyme is considerably weaker than the comparable binding of pyridoxal phosphate based on dialysis experiments.

While the earlier studies of the activity of desoxypyridoxine are amply confirmed by these two independent studies, the inhibitory action of pyridoxine phosphate is not only surprising but rather makes one wonder about the significance of the studies on desoxypyridoxine. The various forms of vitamin B₆ differ in their ability to counteract desoxypyridoxine inhibition, which has led to a hypothesis that it interferes with the absorption of vitamin B₆.³⁹ Actually, the data would be equally compatible with any of a variety of other hypotheses. I think a way out of the dilemma posed by the inhibition observed by

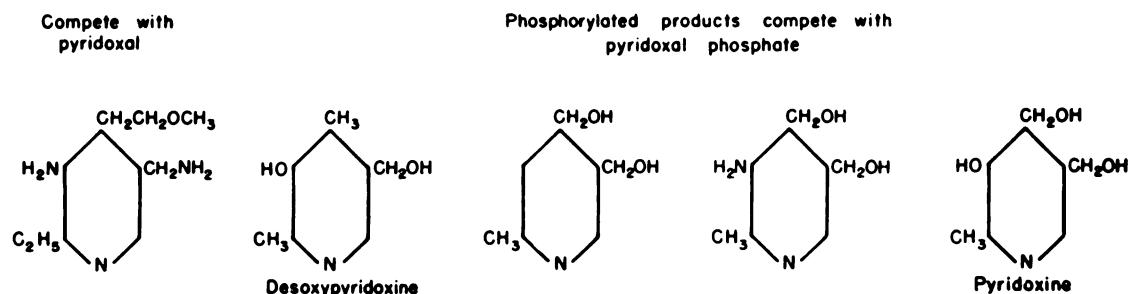


Fig. 3. Antagonists which act either by competing with pyridoxal or whose phosphates compete with pyridoxal phosphate.

aminomethyl pyridine inhibits pyridoxal phosphate formation from pyridoxal and ATP. It is certainly curious that a variety of more subtle changes do not produce inhibitory analogues but that changes are required in the 2, 3, 4 and 5 positions. In the same system, in the absence of pyridoxal, four compounds compete with pyridoxal phosphate after phosphorylation. They all contain the 5-hydroxy methyl group, the presumed site of phosphoryl-

pyridoxine phosphate in rather purified systems would be the real possibility that an enzyme exists which will convert pyridoxine phosphate to pyridoxal phosphate and that this enzyme is present in the living cell. Thus pyridoxine phosphate which can be formed by an enzyme-catalyzed reaction between pyridoxine and ATP is converted to the active coenzyme (impossible with desoxypyridoxine): so the latter remains an inhibitor.

METHOXYPYRIDOXINE

The methoxypyridoxine,^{40,41,42} which has been studied less and not from the point of view of mechanism, and the 5-desoxy compounds are even less well explored.⁴³ As a matter of fact, for several years there has been relatively little widespread interest in vitamin B₆ or its antagonists, and relatively little fundamental work has been done. This attitude arose in part from the lack of spectacular therapeutic success except under restricted conditions and the general attitude that vitamin B₆ deficiency was not ever encountered in man, except under the most extreme circumstances. While the latter concept is at present undergoing a marked revision, to the extent, indeed, that perhaps what we call "normal" is borderline vitamin B₆ deficiency, it still remains that, from the point of view of a therapeutic agent, the fact that vitamin B₆ is concerned with so many basic reactions of amino acids renders it unlikely, at least according to theory, that sufficient specificity will be found to permit the specific therapy necessary. I have pointed out how what is known of the action of 4-desoxypyridoxine cannot be entirely explained by its action as a simple vitamin B₆ antagonist.

This would suggest that there are possibilities for therapy among compounds of this group, and that perhaps unexpected specificity may be found, especially if one does not lean too heavily upon vitamin B₆ antagonism *per se*. However, such studies remain for the future. Perhaps it is indicative that a clinically successful chemotherapeutic agent, isonicotinic hydrazide, is a vitamin B₆ antagonist.^{44,45} Our own studies agree that with respect to tryptophanase,⁴⁴ isonicotinic hydrazide is an excellent antagonist of pyridoxal phosphate, although we do not, as is reported,⁴⁵ find that it antagonizes pyridoxal phosphate in amino acid decarboxylation. Its action in our hands²⁷ is not merely that of the hydrazide combining with the 4-aldehyde of pyridoxal phosphate. However, certainly isonicotinic hydrazide is known for its action in the tubercle organism,⁴⁶ and in this case its activity either in culture⁴⁷ or against the disease

in the mouse is not reduced by vitamin B₆.^{47,48,49} and its action in the tubercle organism, therefore, appears to be based on some other property. Some of the side effects produced by isoniazid, however, are cleared up by the administration by pyridoxine,^{48,49,50} when these are also cleared up by the withdrawal of isoniazid.

There is another even more surprising vitamin B₆ antagonist, and this is the pyrimidine moiety of thiamine. Injection of this substance causes convulsion in mice or rats, and this effect is completely eliminated by administration of vitamin B₆.⁵¹ The phosphorylated pyrimidine seems to be a potent antagonist of pyridoxal phosphate.⁵² A few other vitamin B₆ antagonists⁴ have been reported to my knowledge, but little further has been done with them.

CONCLUSIONS

There seems to be a time and tide in scientific development, as there is alleged to be in the affairs of men, and with respect to vitamin B₆ we seem to be, after a period of relative quiescence, at the threshold of a resurgence of interest. At such a point it is frequently futile to discuss either past successes or failures or future possibilities, because a new concept or a new orientation may illumine with significance what is now darkened with neglect. One can sense, I think, that vitamin B₆ is at this stage, and I would suppose that in five years from now something of real clinical significance may emerge and a discussion of vitamin B₆ antagonism be thus of much more significance. At any rate, this is my picture of the mode of action and therapeutic implication of the vitamin B₆ antagonists known as of today, and I find it prudent to make no predictions for the future whatsoever, certain in the knowledge that no matter what one might predict at this point, experiment would be certain to demonstrate that the facts and their significance are otherwise.

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