THIAMINE AND THE NERVOUS SYSTEM: AN OVERVIEW

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Thiamine deficiency and its effects on the nervous system have been subjected to intensive investigation since 1882, when Admiral Kanehiro Takaki, medical officer of the Japanese Navy and son of an officer of the Imperial Palace Guard in Kyoto, sought to unravel the mysteries of Kakke (beriberi), which was decimating the crews of Japanese warships.

After the studies of Sir Rudolph Peters and his colleagues in the 1930s had revealed the role of thiamine and its phosphoric esters as a cofactor in intermediary carbohydrate metabolism, it seemed most logical to attempt to link the neurological manifestations of thiamine deficiency to a failure of energy metabolism. The importance of thiamine in two reactions of the hexose monophosphate shunt, elucidated 20 years later, provided yet another possible biochemical explanation for the development of neurological symptoms and signs. However, although it has been possible to correlate neurological dysfunction with failure of enzymatic activity within the nervous system and other organs, it has not been possible to ascertain whether the neurological symptoms and signs and the eventual histopathological changes can be attributed to these biochemical events.

An entirely different approach to the problem of thiamine deficiency and neurological dysfunction has been taken by neurophysiologists and neuropharmacologists since the classical observations of Von Murralt and his associates relative to the role of thiamine in the function of excitable membranes as a non-cofactor.

It is the purpose of this presentation to

briefly review the current status of thiamine research as it pertains to the nervous system and to speculate about the pathophysiology of the neurological problems engendered by the dietary deficiency of this vitamin.

First of all, it seems appropriate to once again emphasize the fact that thiamine deficiency in experimental animals produces a clinical syndrome affecting the central nervous system, characterized by ataxia, abnormal postures, and vestibular disturbances. In man the additional symptoms of ophthalmoplegia and an acute confabulatory-amnestic syndrome may be observed. Seizures or convulsions characterized by loss of consciousness and paroxysmal electroencephalographic abnormalities are not part of the clinical picture. In both animals and man a symmetrical, distal, mixed sensory-motor areflexic neuropathy or polyneuritis of varying degrees, accompanied on occasion by autonomic disturbances, is commonly encountered. The term "*polyneuritis*" applies to the involvement of the peripheral nervous system only, while the symptoms of central nervous system dysfunction are more appropriately called "*encephalopathy*." It has become increasingly evident that old concepts regarding thiamine deficiency and the nervous system must be modified in light of relatively new experimental evidence which seems to provide a logical explanation for both the clinical and the pathological events.

There has been a great deal of controversy about the histological changes observed in the *central nervous system* of thiamine-deficient animals. The most recent studies by Robertson (1), Watanabe (2), and others, have dem-

onstrated clearly that in the acute stages of the deficiency state (produced by either the dietary restriction of the vitamin or by the thiamine analogue pyriethamine, which readily produces neurological symptoms) the early tissue changes consist of edematous swelling of astrocytic foot processes, increased permeability of the vasculature to fluorescein. Evans blue, and horseradish peroxidase and splitting of the basement membrane of capillaries in species-specific selected areas of the brain. Most recently, Vick *et al.* (3) showed early splitting of myelin lamellae at the intraperiod line within the brain-stem lesion of thiamine-deficient monkeys. It appears that eventually all of the tissue elements, including dendrites, neuronal perikarya, oligodendrocytes, and myelin sheaths, are involved, and the tissue, when studied by standard light microscopy, appears to have undergone panecrosis. It is of interest that electron micrographic changes have been detected in the nervous system as early as 6 hr after the administration of pyriethamine. Previous communications by Prickett (4), Alexander (5), Collins (6), and Dreyfus (7) have described the chronic changes but have failed to properly portray the sequence of events and the important primary alterations. In the thiamine-deficient *peripheral nervous system*, early, subtle changes in distal axons have been described by Prineas (8). Pathological changes in peripheral myelin, so frequently described as the hallmark of thiamine-deficient neuropathy, most likely represent secondary, more chronic changes. The histopathological changes noted in both the central and the peripheral nervous system appear to be compatible with the functional changes observed in man and in experimental animals. The early ultrastructural changes, indicative of defective cell membrane transport, seem to correlate best with some of the biochemical or biophysical abnormalities caused by thiamine deficiency.

To date, it has not been possible to delineate the factors which underlie the highly selective

and focal nature of the tissue destruction observed in the central nervous system of every animal species and man, regardless of the method by which the deficiency state has been produced—whether by means of dietary deprivation or by the administration of pyriethamine. Work by Cooper (9), Pincus and Grove (10) suggests that the parts of the nervous system which are affected earliest and to the greatest degree tend to have the highest concentrations of thiamine diphosphate under normal circumstances and that progressive thiamine deficiency results in marked depletion of the diphosphate ester in the affected areas. In no other region of the brain does the level of thiamine diphosphate fall as far or as rapidly. Attempts have been made to relate the selective vulnerability of the lateral vestibular nucleus of the deficient rat brain to an unusual microvascular pattern and to the very high rate of oxidative activity of the perivascular glial cells (predominantly astrocytes) noted in that part of the brain stem. As yet no conclusive studies dealing with this problem have been reported.

Thiamine-dependent enzymes in normal and deficient animals have been studied extensively since the pioneering work of Peters. A variety of different biochemical techniques has been utilized to measure enzymatic activity, and the dietary restriction of thiamine has been compared with the pyriethamine-induced disease state. In general, the various reported studies are in agreement as far as the results are concerned; their interpretation, however, differs considerably. During progressive thiamine deficiency, a profound drop in the level of the vitamin occurs, to the point where less than 20% of normal total thiamine remains in the brain of symptomatic animals. Meanwhile, the reduction in the activity of the two dehydrogenases—pyruvic and alphaketoglutaric dehydrogenase—is of the order of less than 40% while no more than 60% of normal transketolase activity is lost. When one compares the loss of enzyme activity in the encephalopathy of thiamine deficiency to

that produced by a number of genetically determined metabolic encephalopathies known to be caused by an enzymatic defect, one realizes that the reduction in enzymatic activity in the tissues or blood of the *symptomatic* homozygote patient afflicted with such a disease is usually very pronounced, sometimes in excess of 80%, while the *asymptomatic* heterozygote may show as much as a 50% reduction in enzymatic activity. This fact alone casts serious doubts on the importance of enzymatic failure as the major cause of impaired neurological function in the encephalopathy of thiamine deficiency.

It has been noted by Hollowach *et al.* (11) that substrates of the affected enzymes, *i.e.*, pyruvate, α -ketoglutarate, xylulose, and 6-phosphogluconate, pile up in the brain of thiamine-deficient animals while the biochemical consequences of enzymatic failure tend to be negligible: the reduced form of glutathione, NADPH, and acetylcholine levels are either normal or slightly reduced, while ATP concentrations and the lipid composition of the deficient brain are normal. It is, therefore, quite conceivable that the thiamine-deficient brain utilizes alternate metabolic pathways to protect itself against the pile up of potentially harmful substrates.

Since it appears less and less likely that the central nervous system manifestations of thiamine deficiency are engendered by the failure of thiamine-dependent enzymes, other pathophysiological mechanisms must be considered. It seems well established that, in addition to its function as a coenzyme, thiamine is involved in some aspect of the function of neural membranes. Von Muralt (12) first introduced the idea that thiamine plays an important role in the sodium transport system of the nervous system. The experimental evidence which he and his co-workers presented over 20 years ago has been confirmed and amplified by others. The details of how thiamine acts in this rather complex system remain to be worked out.

The evidence can be summarized as follows:

electrical stimulation of central and peripheral nerve preparations results in the release of thiamine. The same can be achieved by using neuroactive agents, such as acetylcholine, ouabain, tetrodotoxin, and LSD. Pyriethamine, an antimetabolite of thiamine, has a profound *in vitro* effect on the electrical activity of isolated preparations of neural tissue. Thiaminase, an enzyme obtained from fish and fern extracts which cleaves the thiamine molecule, has a similar effect. The administration of pyriethamine causes the displacement of thiamine from the tissue, produces neurological signs and symptoms, and results in visible histological changes within a matter of hours without affecting the known thiamine-dependent enzyme systems. Thiamine and the phosphorylases and phosphatases which are responsible for its phosphorylation and dephosphorylation are localized in membranous fractions of neural tissue.

Finally, based on preliminary experimental data, Barchi (13) has theorized that thiamine, or one of its phosphoric esters, plays a role in the initial phase of the action potential by increasing the permeability of the excitable membrane to sodium. It has been postulated that this may be accomplished by the mechanism of phosphorylation of thiamine diphosphate to triphosphate, which may bring about a change in the ionic permeability properties of the membrane. Interference with this system could ultimately lead to abnormal function and visible tissue damage.

The clinical observations made in experimental animals and in patients afflicted with thiamine deficiency could be explained by a failure of membrane permeability or function. The sudden onset of central nervous system dysfunction and its prompt reversal upon the administration of a single dose of the vitamin, the temporary improvement of symptoms following the administration of diphenylhydantoin or calcium noted by Itokawa (14) in deficient pigeons, and the sudden aggravation of symptoms precipitated by a glucose load which probably ties up all of the remain-

ing thiamine, are points in favor of the notion that excitable membranes are failing. In view of the fact that some of the earliest tissue changes observed in thiamine deficiency seem to involve astrocytes, which are known to play a key role in cerebral transport mechanisms, one could logically expect defective electrolyte transport.

It seems most probable that an illness such as Wernicke-Korsakoff syndrome in man, which usually presents in an acute manner and which responds so dramatically to the administration of thiamine, is caused by a failure of membranes. The decrease in blood transketolase activity noted in patients afflicted with Wernicke-Korsakoff syndrome and the restoration of this activity following the administration of thiamine, may be mere coincidence. The effects of thiamine deficiency on other organ systems of the body are most likely caused by a failure of thiamine-dependent enzyme systems. Vitamin deprivation leads to pronounced reduction of enzyme activity in the gastrointestinal tract, liver, kidney, and heart. It is most probably this aspect of the deficiency state rather than the neurological manifestations which proves life-threatening to the patient.

A great deal is known about thiamine and the nervous system, yet much experimental work remains to be done before it is possible to fully understand what thiamine does in the nervous system, how its deficiency causes neurological malfunction, and which of the various known abnormalities is responsible for the ensuing damage. In my presentation,

I have attempted to briefly review some current ideas regarding the function of thiamine in the nervous system. Although research in this field appears to be headed in the right direction, there remain many unanswered questions. New ideas concerning the normal function of the nervous system, development of ingenious research techniques, and a renewed and ever-widening interest in thiamine research will undoubtedly give us the opportunity to discuss this topic once again at some future date.

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