

TRANSKETOLASE THAT IS DEFECTIVE IN TPP BINDING CAN CAUSE A NEUROPSYCHIATRIC DISORDER

The *Wernicke-Korsakoff syndrome*, a striking neuropsychiatric disorder, is caused by a lack of thiamine in the diet of susceptible persons. This disease is characterized by paralysis of eye movements, abnormal stance and gait, and markedly deranged mental function. In particular, a patient with this syndrome is disoriented and has a severely impaired memory. Only a small minority of alcoholics and other chronically malnourished persons develop this disorder. Also, its incidence is much higher among Europeans than among non-Europeans on thiamine-deficient diets. These observations suggest that genetic factors may be important determinants of whether a thiamine-deficient person develops the Wernicke-Korsakoff syndrome. Studies of transketolase from cultured fibroblasts show that this is in fact the case. *Transketolase from patients with the Wernicke-Korsakoff syndrome binds thiamine pyrophosphate tenfold less avidly than does the enzyme from normal persons.* Two other thiamine-dependent enzymes, pyruvate dehydrogenase and α -ketoglutarate dehydrogenase, are normal in this disorder. The abnormality in transketolase becomes clinically evident only when the level of thiamine pyrophosphate is too low to saturate the enzyme. This is a clear-cut example of the interplay between genetic and environmental factors in the production of disease. The Wernicke-Korsakoff syndrome also demonstrates vividly how a reduction in the activity of a single enzyme can have profound neurologic and behavioral consequences.