Summary. Experimental Wernicke's encephalopathy, induced in rhesus monkeys with a diet lacking thiamine (vitamin B₁), is characterized by cavitory necrosis of the striatum as well as a microvascular periventricular lesion of the brain stem such as occurs in man. With high resolution light microscopy and electron microscopy, the primary structural alteration in the brain stem lesion, and probably also in the striatum, appears to be that of widespread "blister" formation due to splitting of myelin at the intraperiod line. Microvascular alterations were minimal, even in the most severely affected regions. It is the myelin blisters which give rise to the spongy texture of the neuropil. A similar splitting of myelin has been described in several other experimental encephalopathies, and it is probable that it also occurs in Wernicke's encephalopathy in man.

Key words: Thiamine Deficiency — Wernicke's Encephalopathy — Rhesus Monkey — Ultrastructure — Myelin.

Introduction

Thiamine (vitamin B₁) deficiency causes Wernicke's encephalopathy in man. This severe, often acute neurological disorder is characterized by ataxia, dementia and ophthalmoplegia (Victor et al.). Untreated, the disease may be fatal. It is most often seen in chronic alcoholism, but occurs in other dietary deficiency states as well. In prolonged starvation without thiamine supplementation the fulminant disease can appear in man in 6 to 8 weeks, and may be precipitated by refeeding (Drenick et al.).

The clinical and pathological syndrome in man has for years provided a paradigm for the concept of selective vulnerability of the central nervous system. The pathological alterations in man consist of well-localized vacuolizations and breakdown of the neuropil, with microglial mobilization and relative sparing of neurons and their processes. Loss of myelin has always been noted to be a prominent feature in the affected areas of the brain. Strikingly selective vulnerability of specific brain regions, especially the mammillary bodies, the medial dorsal nucleus of the thalamus and periventricular structures of the caudal 3rd and the floor of the 4th ventricles is nearly constant (Victor et al.).

The disorder can be induced readily in various mammals and birds (Alexander; Dreyfus and Victor, 1961; Seider and Trautwein). In the rhesus monkey, Rinehart et al. showed by light microscopy that the mammillary bodies were largely spared, and that prominent bilateral, symmetrical cavitory necrosis of the striatum

* Supported by NIH grants 05033-20, NS-09789 and MH-02744, and the Louis Block fund for Research in the Physical and Biological Sciences at the University of Chicago.
** This paper was presented in part at the twenty-sixth annual meeting of the American Academy of Neurology, San Francisco, April 25th, 1974.
(especially the putamen) occurred. We described the correlative light and electron microscopic findings in the rhesus monkey, and presented evidence that the primary structural alteration is a defect in the integrity of myelin (Vick and Schulman, 1974).

Materials and Methods

Four young mature rhesus monkeys were fed a complete diet lacking only thiamine (Teklad Mills Division, ARS/Sprague-Dawley, modified cat. No. 170280, with vitamins increased to levels found in Purina Monkey Chow). Four normally fed animals served as controls. After intravenous pentobarbital anesthesia, the monkeys were sacrificed by intracardiac vascular perfusion of aldehydes, as previously described in detail (Sipe et al.). Blocks for electron microscopy were taken with the aid of a dissecting microscope. Cerebral and cerebellar cortices were sampled, as were the caudate nucleus, putamen, dorsal thalamus (medial dorsal nucleus and pulvinar), hypothalamus (mammillary bodies) and the following brain stem nuclei: oculomotor, abducens, motor trigeminal, hypoglossal, area postrema and the entire vestibular complex. These blocks were further fixed in cacodylate-buffered osmium tetroxide and aqueous uranyl acetate, rapidly dehydrated in graded methanols and propylene oxide, and embedded in durcupan. Sections for light microscopy (1.0 μ) were stained with toluidine blue-0. Sections for electron microscopy (400–700 Å) were mounted on uncoated 75×300 mesh copper grids, stained with both warm uranyl acetate in 50% methanol and lead citrate, and examined with a Philips 200 electron microscope at 40 or 60Kv. The remaining coronal sections, with the small blocks having been removed unilaterally from paired structures, were embedded in celloidin or paraffin. Serial sections were stained with cresyl violet, hematoxylin and eosin and by the Klüver-Barrera methods. These techniques permitted precise anatomical localization of the small blocks taken for durcupan embedding, and hence, close correlation between the tissues prepared by the various methods.

Results

Three monkeys fed the thiamine deficient diet developed neurological signs within 7 to 10 weeks. The fourth was sacrificed at 4 weeks, prior to onset of any clinical manifestations. The neurological defects, which occurred abruptly in all three, and were heralded only by a decreased consumption of the diet for several days, consisted of severe ataxia, impaired righting reflexes and ophthalmoplegia. The ophthalmoplegia in two animals was complete, with ptosis and abnormal pupillary light reflexes; in the other it was partial. Nystagmus was present in one. Disturbance of deep tendon reflexes and sensation were notably absent in all.

The distribution of the lesion was nearly identical in all three animals. In two, grossly visible brownish discoloration, with extensive symmetrical cavitation, was seen in the striatum. In the other, a similar lesion without grossly apparent changes was identified histologically. There were no other gross alterations. Specifically, the mammillary bodies appeared normal and the periventricular brain stem lesions were not grossly evident.

In stained histological sections, lesions were readily visible to the naked eye. We found noteworthy alterations in two regions: the striatum (chiefly the putamen) and the periventricular structures of the aqueduct and fourth ventricle. The mammillary bodies, the dorsal thalamus and the cerebral and cerebellar cortices were normal. Preservation of structure in the brain regions free of pathological alteration was excellent and indistinguishable from that observed in the same regions in the control animals.

The one experimentally fed monkey sacrificed at 4 weeks showed no brain abnormalities and was indistinguishable from the controls.

The Striatal Lesion

In the three animals with encephalopathy, there were bilaterally symmetrical lesions in the neostriatum (Fig.1a). These consisted of roughly circular zones of degeneration situated in the centers of the caudate nucleus and putamen, limited