PYRUVATE DEHYDROGENASE ACTIVITY FOLLOWING ADMINISTRATION OF AN EXCESS OF THIAMINE

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Pyruvate dehydrogenase (PD) is one of the first enzymes for which thiamine diphosphate (TDP) was shown to possess coenzyme activity. The increased level of pyruvic acid (PA) in the blood stream found in the presence of thiamine deficiency was usually associated with inadequate TDP for the formation of the full PD system [8, 9]. Later detailed investigations [2, 6] showed, however, that the PA level in the blood and tissues is determined by several other factors, often unconnected with thiamine. In addition, when the PD activity in the tissues and the PA level in the blood were determined simultaneously, disagreements were found, which greatly confused ideas regarding this field of metabolism [7]. Recently, using various objects, the authors have shown [3] that administration of excessive doses of thiamine stimulates the accumulation of lipids in the tissues, while acute avitaminosis B_1 has the opposite effect [4]. One of the probable mechanisms of the action of thiamine on lipid metabolism may be the regulatory influence of the vitamin on the activity of PD, i.e., the link in which the acetyl radicals are generated for synthesis of lipids from their carbohydrate precursors. One aspect of this mechanism has been adequately studied: thiamine deficiency, however caused, is always accompanied by depression of PD activity. On the other hand, the state of the PD following administration of excess of thiamine has not been adequately studied. This may be because of the widely held view that states of the hypervitaminosis B_1 type do not exist [5].

The object of this investigation was to study the activity of PD following administration of an excess of thiamine to rats.

EXPERIMENTAL METHOD

Experiments were carried out on three groups of rats: group 1) control animals; group 2) rats receiving thiamine subcutaneously in a dose of 1 mg daily for 25-35 days; group 3) rats receiving a single toxic dose of thiamine (650 mg/kg). Between 5 and 8 min later, at the height of the toxic action of the vitamin, the animals were sacrificed by decapitation. In each experiment the experimental and control animals were used simultaneously. The tissues were extracted and homogenized in the cold for subsequent spectrophotometric (in the SE-4 apparatus) determination of the PD activity [5]. The activity of the enzyme was expressed in conventional units of increase of extinction (420 mμ) due to reduced ferricyanide (per 30 min per g fresh tissue).

EXPERIMENTAL RESULTS

In the rats receiving thiamine in a dose of 1 mg daily for 1 month the activty of the enzyme in the liver tissue and the heart muscle rose significantly (see Table). This might suggest the adaptive synthesis of an increased quantity of apoenzyme proteins in connection with the prolonged adminstration of the vitamin, but after administration of toxic doses of thiamine, when the animals were sacrificed a very short time after administration of the vitamin, the PD in the liver and heart was clearly activated in these animals also. It may be postulated that even after such a short time interval, a large quantity of TDP could be formed in the tissues, but the additional synthesis of apoenzyme proteins in these conditions in improbable.

The PD apoenzyme is known to possess high lability, and it has been shown [10] that its content may fall appreciably in the tissues in chronic avitaminosis B_1 devloping over a long period of time from a lack of the vitamin in the diet. On the other hand, it has been reported [11] that the PD of normal animals is

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Activity of Pyruvate Dehydrogenase (in Extinction Units/g Tissue/30 min).

Index	Control		Hypervitaminosis B_1		Toxic doses	
	Liver	Heart	Liver	Heart	Liver	Heart
n	9	9	9	6	8	8
$M \pm m$	1,86±0,27	1,27±0,15	2,80±0,30	2,30±0,16	3,56±0,42	3,30±0,24
P	—	—	0,05	0,01	0,001	0,001

readily activated in vitro by the addition of TDP, and that in avitaminosis B_1 caused by hydroxythiamine or pyrithiamine, this enzyme system may be reactivated by TDP to a higher level than in normal animals. These facts suggest either that a small excess of PD apoenzyme protein is constantly present in the tissues, or that certain proteins capable of unilateral activation depending on the nature of the added coenzyme may be polyapoenzyme in nature [12]. Whatever the possible mechanisms of activation of PD by thiamine, increased administration of the precursor of the coenzyme specifically activates the corresponding enzyme system. This is already known in relation to certain other enzymes [1], and it may therefore be concluded from the results obtained in the present experiments with thiamine that the link between the vitamin and lipid metabolism, as determined previously [3, 4], may be achieved partly through the PD system.

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