Cardiac Malic Enzyme in Friedreich’s Disease

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ABSTRACT: We measured the activity of cytosolic and of mitochondrial malic enzyme in the hearts from 4 patients with Friedreich’s disease and from two non-ataxic control subjects. There was a wide variability in the results and the slight overall decreases in both enzyme activities were not considered to be statistically significant. From these and other results, we conclude that deficient mitochondrial malic enzyme activity is not a constant or primary feature of Friedreich’s disease.

RESULTS

As can be seen in Table 1, “total” malic enzyme activity is slightly (-33%) lower in the ataxic group. This is due equally to a decrease in mitochondrial (-25%) and cytosolic activity (-34%). There is a wide variability in the results which makes them non significant statistically. However, when ataxic values are compared to their respective mean control values for mitochondrial activity, two Friedreich cases have higher activities (+24%, +45%) and two, lower activities (-83%, -52%). Only one of the latter is within the range of the deficit reported by Stumpf and his collaborators (1982) i.e. circa 90% decrease.

SUBJECTS AND METHODS

Hearts were obtained at autopsy (and kept frozen) from 3 patients (2 males, I female) with the typical signs and symptoms of Friedreich’s disease as defined by Geoffroy et al. (1976) and from one patient with the slow progression form of the disease (female) (Barbeau et al., 1984). The pathology and histories of the cases were previously described (Lamarche et al., 1980). The brains from two of these patients were studied independently by Stumpf and his collaborators. Ages at death ranged from 18 to 38 and duration of the ataxic illness from 11 to 31 years. A severe symmetrical hypertrophic cardiomyopathy was present in all cases (Lamarche et al., 1980). Control hearts were obtained from the pathology department of the Hôtel-Dieu Hospital in Montreal. One was from a man age 55 who died from intestinal neoplasia and the other from a man age 39 who died accidentally. These hearts were normal to gross pathology. Delay between death and autopsy did not exceed 14 hours in all cases.

Malic enzyme activity was estimated in cytosol and mitochondrial fractions from the hearts according to the protocol recommended by Bottachi and Di Donato (1983) as modified by Melançon et al. (1984) in this issue (for details see that paper).

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These results are better illustrated in Fig. 1, where the wide variability is apparent. One clear pattern emerges from our results: an inverse relationship between cytosolic and mitochondrial values. The lower the cytosolic activity of malic enzyme, the higher the mitochondrial activity. This suggests an exchange between compartments and perhaps a defective mitochondrial membrane barrier, as proposed by Barbeau (1980).

**DISCUSSION**

Malic enzyme (Fig. 2) is an inducible enzyme whose function is still not clearly understood. It has been known to exist in mammalian tissue in at least two forms: soluble (cytosolic) and mitochondrial. In the human, the cytosolic enzyme is found in all tissues except red cells and serum. It is even present in fibroblasts. The mitochondrial enzyme is seen in brain, kidney, heart muscle, liver and cultured fibroblasts. Like the cytosolic enzyme, mitochondrial malic enzyme is a tetramer. It can show marked polymorphism in human tissue. Absolute activity of the various forms of malic enzyme vary greatly from tissue to tissue: in adrenal medulla and white adipose tissue malic enzyme is located exclusively within the extra-mitochondrial compartment. In liver, 95% of the activity is extra-mitochondrial and only 5% intra-mitochondrial. In heart, 30% of the enzyme activity is usually extra-mitochondrial and 70% intra-mitochondrial (Brdiczka and Pette, 1971).

Although there is a considerable variability in our present results, it is obvious that a major defect in mitochondrial malic enzyme activity in this target tissue is not a constant feature of our cases, even when differences in age with the controls are taken into account. Only one of the hearts had markedly decreased activity of the mitochondrial malic enzyme in the range reported by Stumpf et al. (1982). There are no distinguishing clinical features between the 4 cases that we can detect, except a longer duration of the illness in the atypical variant. All are clearly "classical" cases of Friedreich.

It is recognized that the available number of studied ataxic hearts is low, but it is unlikely that added cases would markedly alter the findings. Our results in heart tissue are supported by the findings of Stumpf et al. (1982, 1983). Our conclusions of a probable secondary defect are nevertheless closer to those of Bottachio and Di Donato (1983).

When the present findings are taken in conjunction with our results in cultured fibroblasts (see Melançon et al., this issue) which were essentially normal, one must conclude that, unless unsuspected methodological differences were present, mitochondrial malic enzyme deficiency is not a constant marker of Friedreich's disease as we define it (Geoffroy et al., 1976). The variability of results would tend to favor a manifestation secondary to the primary defect, perhaps as a result of a membrane defect (Barbeau, 1980). This would explain why it is possible, in some cases, to find very low activity of the enzyme, and in others essentially normal values. We have no good reasons to propose to explain the implied discrepancies with the findings of Stumpf et al. (1982, 1983). Our conclusions of a probable secondary defect are nevertheless closer to those of Bottachio and Di Donato (1983).

In view of the proposed role of polyunsaturated fatty acids in the pathophysiology of Friedreich's symptoms (Barbeau, 1980, 1982), it may be pertinent to investigate the diet and therapy of the patients during the months preceding death before determining malic enzyme activity. In this respect, two of our ataxic patients had been taking Lecithin (6 to 12 grams daily) for some months (see Barbeau, 1978; Melançon et al., 1982). Their
mitochondrial malic enzyme activity in the heart was +24% and -52% of their respective controls.

Finally another facet of the problem could be considered. It is known that the mitochondrial malic enzyme, but not the cytosolic enzyme, is activated by succinate and aspartate (Frenkel and Cobo-Frenkel, 1973). The activity of this enzyme may thus increase rapidly under conditions which would favour accumulation of intermediates of the Krebs cycle. Conversely the activity of mitochondrial malic enzyme decreases in the face of a deficiency in Krebs cycle intermediates. In this respect it is worthwhile to remember that the concentrations of aspartic acid were found to be decreased in the brain of Friedreich patients (Huxtable et al., 1979).

ACKNOWLEDGEMENTS

The studies reported in this paper were supported by a grant from “L’Association Canadienne de l’Ataxie de Friedreich”. The authors would like to thank Dr. J. B. Lamarche for the pathological verification, Dr. Serge Melançon for technical suggestions, and Mrs. Nicole Guay-Poirier for typing the manuscript.

REFERENCES


Am Heart J 104: 887-888.