Quebec Cooperative Study
of Friedreich's Ataxia

Amino Acid Changes in Thiamine-Deficient Encephalopathy: Some Implications for the Pathogenesis of Friedreich's Ataxia

R. F. BUTTERWORTH, E. HAMEL, F. LANDREVILLE, AND A. BARBEAU

SUMMARY: *Thiamine-deficient encephalopathy in the rat is characterized by ataxic gait, loss of righting reflex and curvature of the spine. Neurochemical changes include a diminished activity of cerebral pyruvate decarboxylase leading to abnormal pyruvate oxidation. The present study shows that this defective pyruvate oxidation produces a significant depletion of three important amino acid neurotransmitters, namely gamma aminobutyric acid (GABA), glutamic acid, and aspartic acid. Such changes could lead to severe neuronal dysfunction and the observed neurological symptoms of thiamine deficiency. Some implications for the pathogenesis of Friedreich's ataxia are discussed.*

RÉSUMÉ: *L'encéphalopathie produite chez le rat déficient en thiamine se caractérise par une ataxie de la démarche et par la perte du réflexe de redressement (righting reflex). L'activité cérébrale de la pyruvate décarboxylase est diminuée de façon importante et ce changement neurochimique conduit à une oxydation anormale du pyruvate. Le présent travail montre qu'un tel défaut dans l'oxydation du pyruvate produit une diminution significative de GABA, d'acide glutamique et d'acide aspartique, trois acides aminés importants au cerveau. De tels changements seraient probablement à l'origine des symptômes neurologiques observés dans la déficience en thiamine. Nous discuterons des implications possibles dans la pathogénèse de l'ataxie de Friedreich.*

From The Clinical Research Institute of Montreal.

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INTRODUCTION

It has recently been shown that Friedreich's ataxia is associated with certain biochemical abnormalities involving pyruvate metabolism (Barbeau et al., 1976) an abnormally low activity of serum lipoamide dehydrogenase (Melançon et al., 1977; Filla et al., 1978), and diminished activities of the pyruvate and α-ketoglutarate dehydrogenase complexes in various tissues (Blass et al., 1976). The latter finding has, however, not been confirmed by others (Barbeau et al., 1976; Melançon et al., 1978; Stumpf et al., 1978). Abnormalities of amino acid metabolism have also been reported in association with Friedreich's ataxia. These include diminished levels of glutamic and aspartic acids in affected regions of the spinal cord (Robinson et al., 1968), a decreased level of serum aspartic acid (Lemieux et al., 1976), and decreased glutamic acid and gamma aminobutyric acid (GABA) in certain cerebellar nuclei of affected patients (Huxtable et al., 1979, this issue).

Since glutamic and aspartic acids are now considered to be strong candidates as neurotransmitters in the mammalian central nervous system, any changes in their concentrations could lead to severe neuronal dysfunction and resultant neurological abnormalities. To study the possibility of a biochemical link between impaired pyruvate oxidation and the levels of glutamic and aspartic acids in the central nervous system, we have measured the concentrations of several amino acids in regions of the brain, spinal cord and retinae of rats suffering from a thiamine-deficient encephalopathy, a condition in which pyruvate oxidation has been shown to be impaired (Dreyfus and Hauser, 1965; McCandless and Schenker, 1968).

MATERIALS AND METHODS

Thirty six male Sprague-Dawley rats, 190-210 g starting weight, were used for the experiment. From time of arrival all rats received a thiamine-deficient diet (ICN Life Sciences, Nutritional Biochemicals) for a period of three days, after which time they were divided into three treatment groups (as previously described by Gubler et al., 1974):

Group 1. Control rats received 10 μg thiamine in 0.2 ml 0.85% saline per 100 g body weight per day.

Group 2. Thiamine Deficient rats received 0.2 ml 0.85% saline per 100 g body weight per day.

Group 3. Pyrithiamine-treated rats received 10 μg pyrithiamine in 0.2 ml 0.85% saline per 100 g body weight per day.

All rats were maintained throughout the experimental period on the thiamine-deficient diet ad libitum. Injections of saline, thiamine and pyrithiamine were subcutaneous in all cases. Rats were housed individually, had free access to water, and were weighed and fed daily. Conditions of temperature, humidity, and light cycles were kept constant throughout the experiment.

When neurological signs of thiamine deficiency (described in results) were apparent in the pyrithiamine-treated group, a pyrithiamine treated rat was sacrificed along with the appropriate non-symptomatic thiamine-deficient and control animals. Brains were rapidly removed on ice and dissected into the following regions: cerebral cortex, olfactory bulbs, cerebellum, medulla oblongata, hypothalamus, hippocampus, mid-

brain and striatum. Retinae were also dissected out as were cervical, dorsal, and lumbar-sacral segments of the spinal cord. Nervous tissue was stored in liquid nitrogen until the time of assay.

For amino acid assay, each portion of nervous tissue was separately homogenized in 10 vol. $HC10_4$ (0.48 M) and the amino acids GABA, glutamine, glycine, glutamic acid, aspartic acid, and taurine were measured by the double isotope dansyl microtechnique described by Joseph and Halliday (1975). ^{14}C-radiolabelled amino acids and ^{3}H-dansyl chloride were purchased from New England Nuclear. Pyrithiamine and thiamine were obtained from Calbiochem.

RESULTS

1. Neurological Observations

Figure 1 shows the different weight gains in the three treatment groups during the experimental period. The control group displayed a regular weight increase during the 18 days whereas the thiamine-deficient group gained weight normally for the first week, maintained this for 5 days, then started to lose weight during the final period. In neither the control nor thiamine-deficient groups were there any abnormal neurological signs. The pyrithiamine treated group, on the other hand, showed drastic weight loss during the last 4 or 5 days. This weight loss was accompanied by problems of maintaining equilibrium, an ataxic gait, and in some cases convulsions when manipulated by the tail. A more detailed analysis of the abnormality of gait in these animals is described in an accompanying paper (Jolicoeur et al., this issue).

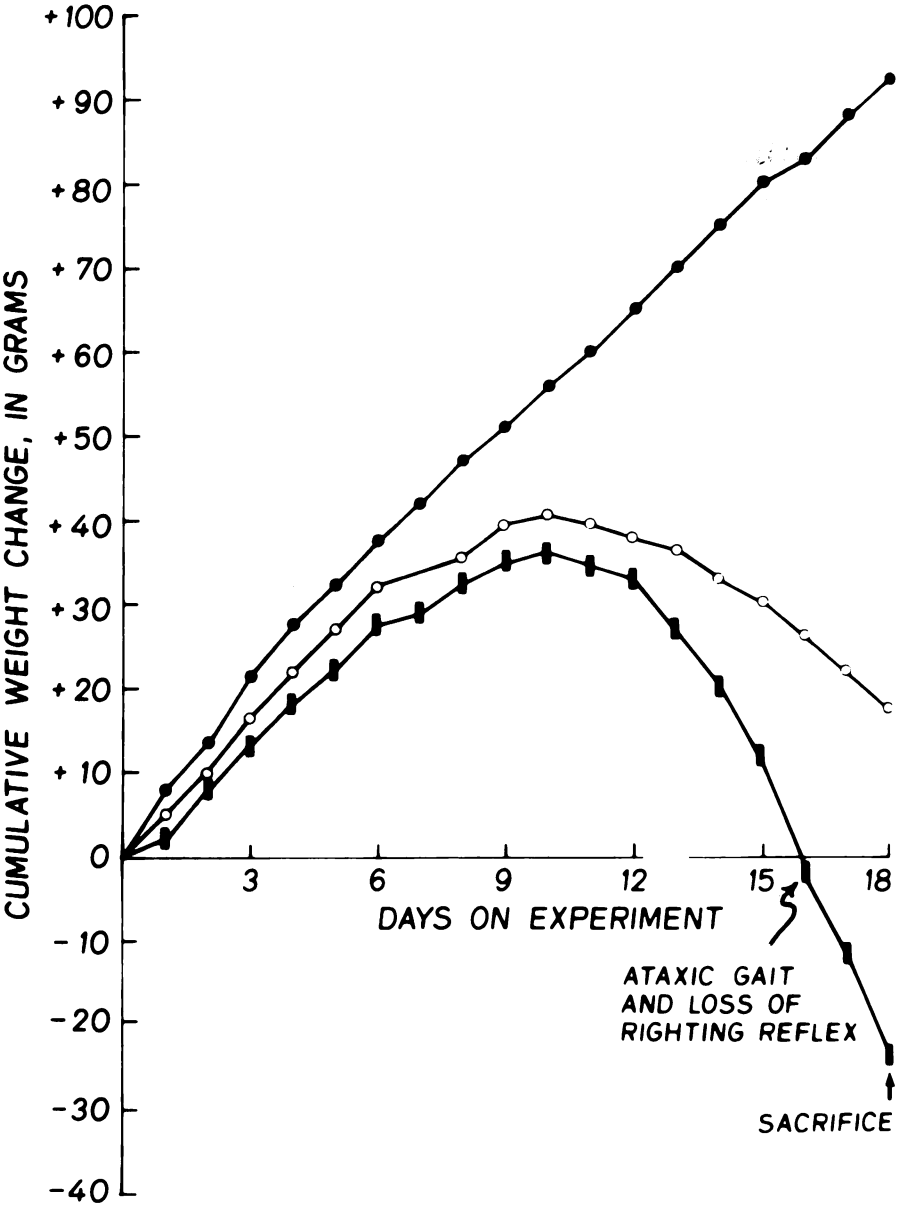

Figure 1 — Mean change in body weight of experimental rats
●——● controls; ○——○ thiamine deficient;
■——■ pyrithiamine-treated

2. Amino Acid Changes

Levels of GABA, aspartic acid, glutamic acid, glutamine, glycine, and taurine in pyrithiamine treated (symptomatic), thiamine deficient (asymptomatic), and control groups of rats are shown in Tables 1-6. Since only the pyrithiamine-treated group are symptomatic, statistically significant differences between amino acid concentrations in pyrithiamine treated rats *vs* both thiamine deficient and controls is most likely to be of importance in the production of neurological symptoms. Such changes include the following: Decreased GABA in medulla oblongata; Decreased aspartic acid in medulla oblongata, cortex and caudate nucleus; Decreased glutamic acid in midbrain, hypothalamus, and hippocampus; Increased glutamine in caudate nucleus.

DISCUSSION

Pyrithiamine is a central thiamine antagonist. It readily crosses the blood-brain barrier and leads to a depletion of brain thiamine and an increased urinary output of the vitamin. The mechanism of action of pyrithiamine is thought to be inhibition of thiamine phosphokinase, the enzyme responsible for the

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TABLE 1

GABA Concentrations

Groups		Brain Region								Spinal Cord			Retina (12)
		Cerebellum (12)	Medulla Oblongata (12)	Midbrain (12)	Cortex (12)	Caudate Nucleus (12)	Hypo-thalamus (12)	Hippo-campus (12)	Olfactory Bulbs (12)	Cervical (8)	Dorsal (8)	Lumbo-sacral (8)	
Pyrithiamine		1.64±0.20	1.44±0.06	3.13±0.31	1.69±0.07	2.60±0.21	3.96±0.10	2.51±0.10	3.22±0.18	1.37±0.05	1.23±0.08	0.81±0.16	2.00±0.09
Thiamine Deficient		1.70±0.16	1.66±0.07	3.35±0.12	1.87±0.11	2.42±0.12	4.48±0.30	2.35±0.18	2.96±0.14	1.15±0.06	1.27±0.07	0.61±0.11	1.86±0.11
Control		2.48±0.14	1.82±0.09	4.81±0.34	2.05±0.05	2.73±0.15	4.52±0.33	2.96±0.16	3.38±0.28	1.40±0.03	1.29±0.12	0.56±0.08	2.20±0.12
p	Pyr./Cont.	*	*	*	*	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	Th.Def./Cont.	*	N.S.	*	N.S.	N.S.	N.S.	N.S.	N.S.	*	N.S.	N.S.	N.S.
	Pyr./Th.Def.	N.S.	*	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	*	N.S.	N.S.	N.S.

TABLE 2

Aspartic Acid Concentrations

Groups		Brain Region								Spinal Cord			Retina (12)
		Cerebellum (12)	Medulla Oblongata (12)	Midbrain (11)	Cortex (12)	Caudate Nucleus (12)	Hypo-thalamus (11)	Hippo-campus (12)	Olfactory Bulbs (12)	Cervical (8)	Dorsal (8)	Lumbo-sacral (8)	
Pyrithiamine		2.83±0.16	2.02±0.38	3.08±0.34	2.96±0.16	1.63±0.17	3.03±0.12	2.87±0.26	2.61±0.21	3.26±0.61	2.81±0.40	2.90±0.10	2.25±0.17
Thiamine Deficient		3.17±0.21	3.38±0.27	3.91±0.38	3.84±0.32	2.33±0.23	3.83±0.40	2.69±0.21	3.55±0.23	3.15±0.23	3.35±0.45	2.99±0.21	2.39±0.14
Control		3.55±0.20	3.84±0.18	6.00±0.35	4.04±0.13	2.21±0.13	5.34±0.39	3.62±0.37	3.17±0.33	2.79±0.23	3.96±0.52	2.45±0.17	2.52±0.12
p	Pyr./Cont.	N.S.	*	**	**	*	**	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	Th.Def./Cont.	N.S.	N.S.	*	N.S.	N.S.	**	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	Control	N.S.	*	N.S.	*	*	N.S.	N.S.	*	N.S.	N.S.	N.S.	N.S.

TABLE 3

Glutamic Acid Concentrations

Groups		Brain Region								Spinal Cord			Retina (12)
		Cerebellum (12)	Medulla Oblongata (12)	Midbrain (12)	Cortex (12)	Caudate Nucleus (12)	Hypo-thalamus (12)	Hippo-campus (12)	Olfactory Bulbs (12)	Cervical (8)	Dorsal (8)	Lumbo-sacral (8)	
Pyrithiamine		9.09±0.22	4.07±0.44	6.16±0.22	10.12±0.30	8.33±0.50	5.08±0.33	9.74±0.25	6.18±0.33	3.80±0.19	2.86±0.20	4.20±0.24	3.84±0.41
Thiamine Deficient		10.08±0.31	4.65±0.46	7.92±0.29	10.32±0.43	9.44±0.26	7.62±0.18	11.52±0.45	7.09±0.33	4.33±0.51	3.40±0.30	4.56±0.19	3.37±0.27
Control		9.86±0.20	5.03±0.50	8.27±0.37	11.76±0.38	8.81±0.37	7.10±0.29	10.97±0.25	6.91±0.35	4.13±0.08	3.44±0.47	4.22±0.26	4.24±0.38
p	Pyr./Cont.	N.S.	N.S.	*	*	N.S.	**	*	N.S.	N.S.	N.S.	N.S.	N.S.
	Th.Def./Cont.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	Pyr./Th.Def.	*	N.S.	**	N.S.	N.S.	**	**	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE 4

Glutamine Concentrations

Groups		Brain Region								Spinal Cord			
		Cerebellum (12)	Medulla Oblongata (12)	Midbrain (12)	Cortex (12)	Caudate Nucleus (12)	Hypo-thalamus (12)	Hippo-campus (12)	Olfactory Bulbs (12)	Cervical (8)	Dorsal (8)	Lumbo-sacral (8)	Retina (12)
Pyrithiamine		6.12±0.19	2.82±0.26	6.72±0.20	5.30±0.17	6.41±0.17	5.86±0.17	5.73±0.20	4.90±0.24	3.31±0.16	2.87±0.16	2.60±0.16	1.98±0.12
Thiamine Deficient		5.62±0.19	2.55±0.21	5.21±0.21	4.95±0.24	5.32±0.17	5.57±0.36	5.20±0.17	4.94±0.21	2.94±0.09	3.06±0.27	2.11±0.08	1.61±0.07
Control		5.47±0.11	2.57±0.23	5.98±0.17	4.89±0.28	5.44±0.10	5.35±0.22	5.02±0.18	5.03±0.35	3.17±0.10	3.97±0.50	2.36±0.14	2.07±0.13
p	Pyr./Cont.	N.S.	N.S.	N.S.	N.S.	**	N.S.	*	N.S.	N.S.	N.S.	N.S.	N.S.
	Th.Def./Cont.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	**
	Pyr./Th.Def.	N.S.	N.S.	**	N.S.	**	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	**

TABLE 5

Glycine Concentrations

Groups		Brain Region								Spinal Cord			
		Cerebellum (12)	Medulla Oblongata (12)	Midbrain (12)	Cortex (12)	Caudate Nucleus (12)	Hypo-thalamus (12)	Hippo-campus (12)	Olfactory Bulbs (12)	Cervical (8)	Dorsal (8)	Lumbo-sacral (8)	Retina (12)
Pyrithiamine		1.00±0.08	2.62±0.28	1.71±0.09	1.23±0.05	1.26±0.09	1.61±0.18	1.33±0.05	0.46±0.07	3.25±0.07	3.04±0.16	4.59±0.21	1.45±0.08
Thiamine Deficient		0.97±0.08	2.72±0.28	1.58±0.08	1.11±0.04	1.16±0.09	1.60±0.10	1.25±0.06	0.74±0.05	3.21±0.14	3.55±0.48	4.11±0.10	1.59±0.07
Control		1.04±0.07	2.78±0.33	1.78±0.06	1.14±0.04	1.21±0.10	1.78±0.23	1.31±0.05	0.47±0.04	3.13±0.08	3.30±0.47	4.12±0.20	1.58±0.09
p	Pyr./Cont.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	Th.Def./Cont.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	**	N.S.	N.S.	N.S.	N.S.
	Pyr./Th.Def.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	**	N.S.	N.S.	N.S.	N.S.

TABLE 6

Taurine Concentrations

Groups		Brain Region								Spinal Cord			
		Cerebellum (12)	Medulla Oblongata (12)	Midbrain (12)	Cortex (12)	Caudate Nucleus (12)	Hypo-thalamus (12)	Hippo-campus (12)	Olfactory Bulbs (12)	Cervical (8)	Dorsal (8)	Lumbo-sacral (8)	Retina (12)
Pyrithiamine		3.04±0.21	1.92±0.12	1.78±0.11	3.31±0.20	6.16±0.38	1.57±0.24	4.80±0.32	10.66±0.57	1.60±0.22	0.55±0.08	0.40±0.17	20.51±1.29
Thiamine Deficient		3.36±0.26	2.19±0.09	1.69±0.15	4.13±0.16	5.70±0.46	1.53±0.21	5.41±0.38	9.85±0.48	1.53±0.25	0.74±0.17	0.55±0.12	19.94±1.12
Control		3.33±0.16	2.07±0.15	1.97±0.18	4.56±0.36	6.22±0.40	1.41±0.20	4.63±0.45	9.58±0.50	1.89±0.15	1.23±0.30	0.77±0.18	20.73±0.90
p	Pyr./Cont.	N.S.	N.S.	N.S.	*	N.S.	N.S.	N.S.	N.S.	N.S.	*	N.S.	N.S.
	Th.Def./Cont.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	Pyr./Th.Def.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

TABLES 1 to 6: — Amino acid levels are expressed in μmole per g wet weight and are presented in the upper part of the table. Values are the mean of triplicate determinations for each animal. Numbers in parentheses represent the number of animals used in each of the 3 groups. Data was analysed by means of a one way ANOVA for the 3 groups of animals in each of the 12 regions. Post hoc Dunnett and Tukey (a) tests were performed when significant differences were revealed by a given analysis of variance. p values obtained from these tests are shown in the lower part of the table; * $p < 0.005$, ** $p < 0.01$, N.S. Not significant.

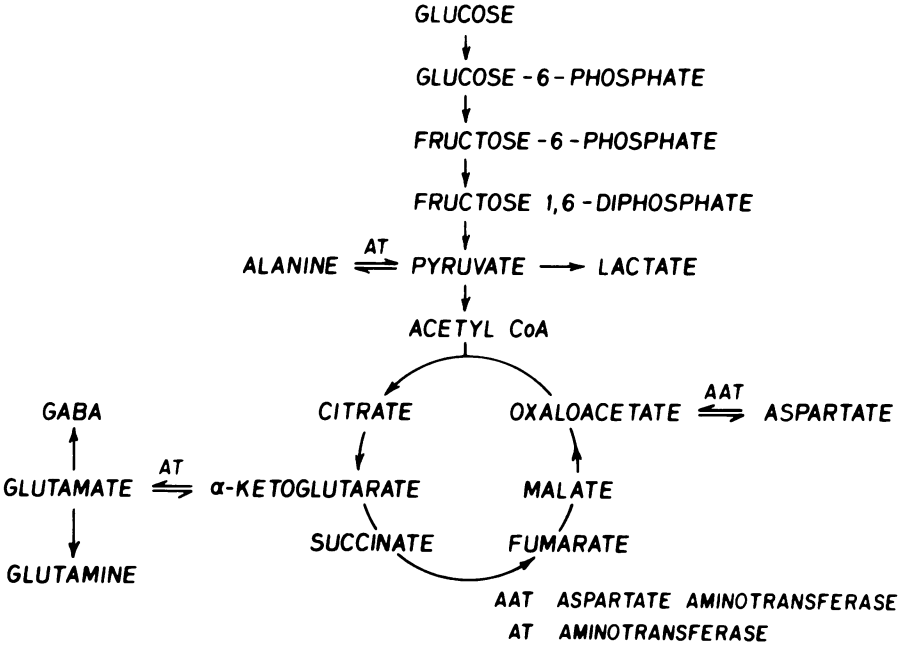
conversion of thiamine to thiamine pyrophosphate (TPP). It has been shown that whole brain activities of the TPP — dependent pyruvate dehydrogenase (PDH) and α-keto-glutarate dehydrogenase (α-KGDH) complexes are decreased by 50% in symptomatic pyrithiamine-treated rats (Gubler, 1961). Similar decreases of activities of these enzymes were reported in the brains of pyrithiamine treated mice (Hollowach, 1968), in addition to increased levels of brain pyruvate and α-ketoglutarate. These findings are consistent with the observed decreased activity of the PDH and αKGDH complexes (see Figure 2).

The modifications of GABA, glutamic acid, and aspartic acid resulting from pyrithiamine treatment may be explained in terms of diminished entry of pyruvate into the tricarboxylic acid cycle, resulting in impaired synthesis of the amino acids. Conversely, it is conceivable that these amino acids may be consumed as an alternative energy source such as has been shown to take place during the neonatal period (Devivo et al., 1975), under certain pathological conditions (Owen et al., 1967), and in *in vitro* experiments in which the supply of glucose to the brain is restricted (Mukherji et al., 1971). A selective depletion of these key amino acids could then lead to severe neuronal dysfunction resulting in the observed neurological symptoms associated with thiamine deficiency.

TABLE 7

Neurological and Biochemical Similarities between Friedreich's Ataxia and Thiamine Deficiency in Rats

	Thiamine Deficiency in Rats	Friedreich's Ataxia
Neurological	— Ataxia (neuropathy) — Curvature of the spine — Nystagmus — Cardiac abnormalities	— Ataxia — Neuropathy — Scoliosis — Nystagmus — Cardiomyopathy — Diabetes
Biochemical	— Glucose intolerance — Abnormal insulin response — Brain PDH and αKGDH activities diminished — Brain glutamate, aspartate and GABA diminished	— Glucose intolerance — Abnormal insulin response — Pyruvate intolerance to oral glucose load — Fibroblast PDH and αKGDH activities diminished (?) — Spinal cord glutamate and aspartate diminished — Cerebellar glutamate, GABA diminished (see this issue)



Metabolic pathways of labelled glucose in adult brain.

Figure 2 — Metabolic pathways of labelled glucose in adult brain.

These results are particularly interesting because thiamine-deficient encephalopathy in the rat shows many neurological and biochemical similarities to Friedreich's ataxia (see Table 7). For example, in addition to the ataxia, characteristic of prolonged thiamine deprivation, both curvature of the spine (scoliosis and cardia abnormalities, two cardinal features of Friedreich's ataxia, are also reportedly

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present (Warnock et al., 1968; Iwata et al., 1968).

Friedreich's ataxia is accompanied by clinical diabetes in 20% of patients, glucose intolerance in a further 20-30%, and abnormal insulin responses in 60% of patients studied (Shapcott et al., 1976). Similar glucose intolerance and insulin abnormalities have been reported in thiamine deficient encephalopathy in the rat (Iwata et al., 1974; 1970). The diminished activities of the PDH and αKGDH complexes, accompanied by increased pyruvate levels have been found in cases of intermittent cerebellar ataxia in children (Lonsdale et al., 1969; Blass et al., 1971) and defective pyruvate utilization has been described in Friedreich's ataxia (Barbeau et al., 1976). Whether or not Friedreich's ataxia patients' fibroblasts and platelets have enzymic defects in the PDH and αKGDH complexes is equivocal (Blass et al., 1976; Barbeau et al., 1976; Melançon et al., 1978; Stumpf et al., 1978).

The present studies suggest that defective pyruvate oxidation is accompanied by significant decreases in GABA, glutamic acid, and aspartic acid concentrations in the central nervous system. Whether such changes in amino acid levels are responsible for the neurological symptoms of Friedreich's ataxia is speculative. It is of interest, however, that diminished levels of glutamic acid and aspartic acid in the spinal cord of Friedreich's ataxia patients have been reported (Robinson et al., 1968) and that levels of GABA and glutamic acid appear to be diminished in certain areas of the cerebellum in Friedreich's ataxia (Huxtable et al., this issue).

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REFERENCES

BARBEAU, A., BUTTERWORTH, R. F., NGO, T. T., BRETON, G., MELANCON, S., SHAPCOTT, D., GEOFFROY, G. and LEMIEUX, B. (1976). Pyruvate metabolism in Friedreich's ataxia. Can. J. Neurol. Sci. 3 (4): 379-389.

BLASS, J. P., AVIGAN, J. and UHLENDORF, B. W. (1971). A defect in pyruvate decarboxylase in a child with an intermittent movement disorder. J. Clin. Invest. 49: 423-432.

BLASS, J. P., KARK, P. and MENON, N. K. (1976). Low activities of the pyruvate and oxoglutarate dehydrogenase complexes in five patients with Friedreich's ataxia. N. Eng. J. Med. 295: 62-67.

DEVIVO, D. C., LECKIE, M. P. and AGRAWAL, H. C. (1975). D-β-hydroxybutyrate: a major precursor of amino acids in developing rat brain. J. Neurochem. 25: 161-170.

DREYFUS, P. M. and HAUSER, G. (1965). The effect of thiamine deficiency on the pyruvate decarboxylase system of the central nervous system. Biochim. Biophys. Acta 104: 78-84.

FILLA, A., BUTTERWORTH, R. F., GEOFFROY, G., LEMIEUX, B. and BARBEAU, A. (1978). Serum and platelet lipoamide dehydrogenase in Friedreich's ataxia. Can. J. Neurol. Sci. 5(1): 111-114.

GUBLER, C. J. (1961). Studies on the physiological functions of thiamine. J. Biol. Chem. 236 (12): 3112-3120.

GUBLER, C. J., ADAMS, B. L., HAMMOND, B., EN CHUAN YUAN, GUO, S. M. and BENNION, M. (1974). Effect of thiamine deprivation and thiamine antagonists on the level of γ-aminobutyric acid on 2-oxoglutarate metabolism in rat brain. J. Neurochem. 22: 831-836.

HOLLOWACH, J., KAUFFMAN, F., IKOSSI, M., THOMAS, C. and McDOUGAL, D. B. (1968). The effects of a thiamin antagonist, pyrithiamin, on levels of selected metabolic intermediates and on activities of thiamin-dependent enzymes in brain and liver. J. Neurochem. 15: 621-631.

IWATA, H., WATANABE, K., NISHIKAWA, T. and OHASHI, M. (1968). Effects of drugs on behavior, heart rate and catecholamine levels in thiamine-deficient rats. Eur. J. Pharm. 6: 83-89.

IWATA, H. and NISHIKAWA, T. (1970). Insulin intolerance in thiamine-deficient rats. Letters to the Editor, J. Pharm. Pharmac. 22: 645-646.

IWATA, H., BABA, A., BABA, T. and NISHIKAWA, T. (1974). Glucose intolerance in thiamine-deficient rats. J. Pharm. Pharmac. 26: 707-710.

LEMIEUX, B., BARBEAU, A., BERONIADE, V., SHAPCOTT, D., BRETON, G., GEOFFROY, G. and MELANCON, S. (1976). Amino acid metabolism in Friedreich's ataxia. Can. J. Neurol. Sci. 3(4): 373-379.

LONSDALE, D., FAULKNER, W. R., PRICE, J. W. and SMEBY, R. R. (1969). Intermittent cerebellar ataxia associated with hyperalaninuria. Pediatrics 43(6): 1025-1034.

McCANDLESS, D. W. and SCHENKER, S. (1968). Encephalopathy of thiamine deficiency: studies of intracerebral mechanisms. J. Clin. Invest. 47: 2268-2280.

MELANCON, S. B., POTIER, M., DAILLAIRE, L., GEOFFROY, G., LEMIEUX, B. and BARBEAU, A. (1977). Serum lipoamide dehydrogenase in Friedreich's ataxia. Pediatr. Res. 11: 460.

MELANCON, S. B., POTIER, M., DALLAIRE, L., GEOFFROY, G., GRENIER, B., LEMIEUX, B., GEOFFROY, G. and BARBEAU, A. (1978). Lipoamide dehydrogenase in Friedreich's ataxia fibroblasts. Can. J. Neurol. Sci. 5(1): 115-119.

MUKHERJI, B., TURINSKY, J. and SLOVITER, H. A. (1971). Effects of perfusion without glucose on amino acids and glycogen of perfused rat brain. J. Neurochem. 18: 1783-1785.

OWEN, O. E., MORGAN, A. P., KEMP, H. G., SULLIVAN, J. M., HERRERA, M. G. and CAHILL, G. F. (1967). Brain metabolism during fasting. J. Clin. Invest. 46: 1589-1595.

ROBINSON, N. (1968). Chemical changes in the spinal cord in Friedreich's ataxia and motor neurone disease. J. Neurol. Neurosurg. Psychiat. 31: 330-333.

SHAPCOTT, D., MELANCON, S. B., BUTTERWORTH, R. F., KHOURY, K., COLLU, R., BRETON, G., GEOFFROY, G., LEMIEUX, B. and BARBEAU, A. (1976). Glucose and insulin metabolism in Friedreich's ataxia. Can. J. Neurol. Sci. 3(4): 361-365.

STUMPF, D. A. and PARKS, J. K. (1978). Friedreich's ataxia: Normal pyruvate dehydrogenase complex activity in platelets. Ann. Neurol. 4: 366-368.

WARNOCK, L. G. and BURKHALTER, V. J. (1968). Evidence of malfunctioning blood brain barrier in experimental thiamine deficiency in rats. J. Nutr. 94: 256-260.