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BRAIN METABOLISM AND ELECTROGENESIS IN PHENYLKETONURIA

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Phenylketonuria is an autosomal recessive disease due to the deffect of enzyme phenylalaninehydroxylase which metabolizes aminoacid phenylalanine to tyrozine (18). Rapid postnatal elevation of phenylalanine in the blood may soon exceed the norm by 20 up to 30 times. Phenylalanine actively passes the hematoencephalic barrier and leads to severe neural retardation with low IQ (1, 2). Hyperphenylalaninemia may be also responsible for the imbalance of the protein metabolism (4).

In the present paper we investigated the metabolism of aminoacids of the brain in rats with experimental hyperphenylalaninemia. In the second part we examined the effect of local application of phenylalanine (FA) and of phenylpyruvic acid (FP) to the brain cortex of rats.

MATERIAL AND METHODS

To ten fife day old rats there was applied either combination of DL alfa-methylphenylalanine and L phenylalanine (MEPH 2.4 and PHE 5.2 mMol · kg^{-1}) twice a day, or combination of DL p-chlorphenylalanine and L phenylalanine (pC1PHE 0.9 and PHE 5.2 mMol · kg^{-1}) once a day. After 5 days the animals were decapitated. Tissue extraction and biochemical analysis were described in detail in the previous paper (21).

The second part of experiments was performed with 21 days old rats anesthetised with pentobarbital. Electrocorticogram was registered by means of silver ball electrodes placed to intact pia mater bilaterally to the right and to the left hemisphere. Small strips of filter paper soaked with warm solution either of phenylalanine, phenylpyruvate or physiological solution were placed closely to the electrodes.

RESULTS

Application of PHE leads to rapid elevation of this aminoacid in the blood and in the brain followed by a slow decline. Addition of MPHE prolongs this effect. Hyperphenylalaninemia leads to important changes of metabolism of other brain aminoacids (Tab. 1). Especially striking is the elevation of glycine (Fig. 1). Significantly are elevated tyrosine

Tab. 1 Brain aminoacids in hyperphenylalaninemic rats (μMol/1g wet weight)

Aminoacid	**0.9%**	**pClPHE + PHE**
Glycine	0.085 ± 0.007	1.24 ± 0. 210
Asparagine	1.870 ± 0.107	2.62 ± 0.290
Tyrosine	0.260 ± 0.018	0.33 ± 0.290
Glutamine	5.130 ± 0.533	3.970 ± 0.416
Valine	1.590 ± 0.010	0.106 ± 0.023
Methionine	0.048 ± 0.004	0.034 ± 0.009
Leucine	0.148 ± 0.029	0.103 ± 0.010
Serine	1.150 ± 0.098	1.320 ± 0.243
Alanine	0.726 ± 0.730	0.686 ± 0.046

and asparagine, contrary lower concentration had glutamine, valine, methionine and leucine, concentration of serine and valine was not influenced.

Local application of phenylalanine and especially of its metabolite phenylacetic acid to the brain cortex elicited typical high voltage epileptogenic discharges (Fig. 2).

DISCUSSION

Phenylketonuria is a clinical important metabolic disease with the incidence of 1 : 8,000 deliveries in our country. With regard to weighty consequences of the disease still continues clinical and experimental research (7, 16, 18). Owing to the results there is nowadays possible a prenatal (15, 19) and early postnatal diagnosis (5, 11, 23), detection of asymptomatic heterozygotes and successful dietetic therapy (3, 6, 10, 12, 25).

It is not surprising that phenylketonuria not only blocks the production of tyrosine but influences also the metabolism of other brain aminoacids (8, 13, 20). The elevation of glycine in our experiments approached values which are characteristic for the cogent brain syndrome of nonketotic hyperglycinemia (14). In the case of defective enzyme phenylalanine hydroxylase, phenylalanine can be partially metabolised to phenylpyruvic, phenylbutyric and phenylaceti acid (9). These metabolites manifest itself in the characteristic odour of urine and sweat. Evidently they participate also on varied symptoms of the disease. In our experiments we confirmed their role in epileptogenesis (17, 22, 24).

SUMMARY

Experimental phenylketonuria in young rats leads besides hyperphenylalaninemia to changes of brain aminoacids. Elevation of glycine approaches values characteristic for cogent syndrome of nonketotic hyperglycinemia. Local application of phenylalanine and its metabolites to the brain cortex is epileptogenic.

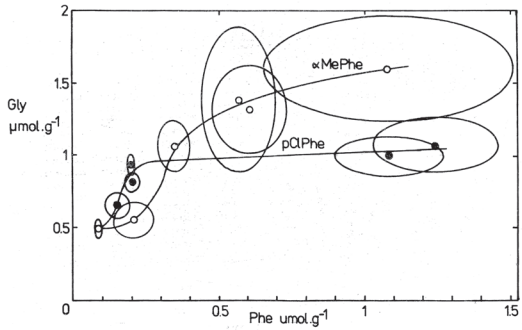

Fig. 1 The dependence of free glycine in the brain to the concentration of free phenylalanine. Elipses present 4 groups of experimental animals. Semiaxes of elipses correspond to ± SD. Empty circles experiments with MEPH + PHE, full circles experiments with pC1PHE (left side) and with pC1PHE + PHE (right side).

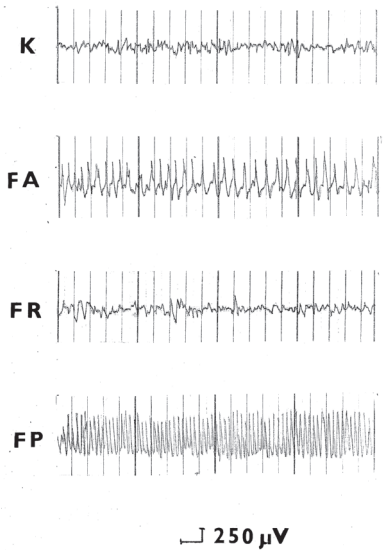

Fig. 2 Electrocorticogram of 21 days old rat. K – control recording FA – phenylalanine, FR – physiological solution, FP – phenylpyruvate.

Metabolismus a elektrogeneze mozku u fenylketonurie

SOUHRN

Experimentální fenylketonurie vyvolaná u mláďat potkanů vede kromě hyperfeylalaninemie ke změně spektra aminokyselin mozku. Zvýšení glycinu je obdobné syndromu neketotické hyperglycinemie mozku. Lokální aplikace fenylalaninu a jeho metabolitů na mozkovou kůru má epileptogenní účinek.

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