Metabolic Effects of Mixture Containing Branched-Chain Amino Acids and Taurine during Subchronic Poisoning with Barbiturates

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We studied the effect of a mixture containing branched-chain amino acids and taurine on the pool of free amino acids and their derivatives during chronic phenobarbital poisoning. Subchronic barbiturate poisoning produced by daily intraperitoneal injection of phenobarbital caused imbalance in the content of some amino acids in blood plasma and liver of rats. Treatment with the mixture of branched-chain amino acids and taurine normalized the content of amino acids in the liver and blood plasma of animals with subchronic phenobarbital poisoning. The mixture of branched-chain amino acids and taurine corrects metabolic processes and normalized the peripheral pool of amino acids. Our findings extend the range for application of amino acids in clinical practice.

Key Words: *phenobarbital; poisoning; amino acids; liver; blood plasma*

Barbiturates, the most popular anticonvulsants, were introduced into clinical practice in 1912 [2]. Phenobarbital (5-ethyl-5-phenyl-barbituric acid) has a wide range of anticonvulsant activity and belongs to the group of barbiturates with long-lasting effects. Phenobarbital contains the hydroxypyrimidine ring. Similarly to nicotinamide coenzymes, this compound acts as the inhibitor of NADPH dehydrogenases in the respiratory chain. Phenobarbital is a psychoactive compound with high additive potential. Excessive chronic consumption of phenobarbital causes dependence, which results in mental degradation [3]. It is necessary to evaluate the effect of phenobarbital on metabolic processes, including the formation of amino acids and their derivatives. However, we found only few reports on this problem.

Amino acids (in the form of minisols) hold promise for combination therapy of alcohol, narcotic, and psychotropic drug abuse. The major manifestation of metabolic imbalance in these conditions is a deficiency of branched-chain amino acids (BCAA). Additional treatment of patients with these amino acids is of particular interest. Metabolic effects of the mixture consisting of BCAA and taurine should be studied in details, because we previously demonstrated high efficiency of this mixture during alcohol poisoning and withdrawal syndrome. Active components of this mixture are taurine possessing antialcohol activity and BCAA. Transport of aromatic amino acids (precursors of neuroactive compounds) across the blood-brain barrier depends on the content of BCAA.

The therapeutic effect of BCAA L-isoleucine, L-valine, and L-leucine in patients with chronic liver diseases and complicating hepatic encephalopathy is determined by essentiality of BCAA for humans and organ-specific metabolic conversions of branched amino acids in the liver and muscle tissue. L-isoleucine, L-valine, and L-leucine play a key role in gluconeogenesis and energy production during combined injury of the liver and central nervous system. The intermediate metabolism of these amino acids activates processes of detoxification during hepatic insufficiency and encephalopathy [6-8].

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Here we studied the effect of BCAA-taurine mixture on the pool of free amino acids and their derivatives during chronic phenobarbital poisoning.

MATERIALS AND METHODS

Experiments were performed on 24 Wistar rats. Chronic barbiturate poisoning was produced by intraperitoneal injection of phenobarbital in a daily dose of 80 mg/kg for 8 days. The mixture of BCAA and taurine (daily dose of 500 mg/kg) was administered through a gastric tube. Control animals received isotonic NaCl.

The concentration of free amino acids and their derivatives in HCl-extracted liver tissue and blood plasma was measured by the method of ion-exchange chromatography [5].

Changes in the pool of amino acids were analyzed by Student's *t* test and correlation and linear discrimination analyses [4]. The mean indexes in groups were compared by Student's *t* test. The correlations within the groups were significant at $|r|=0.78$ or higher. The significance of indexes in a sample was determined by Fischer *F* test. Intergroup differences were estimated by classification matrixes and position of groups and

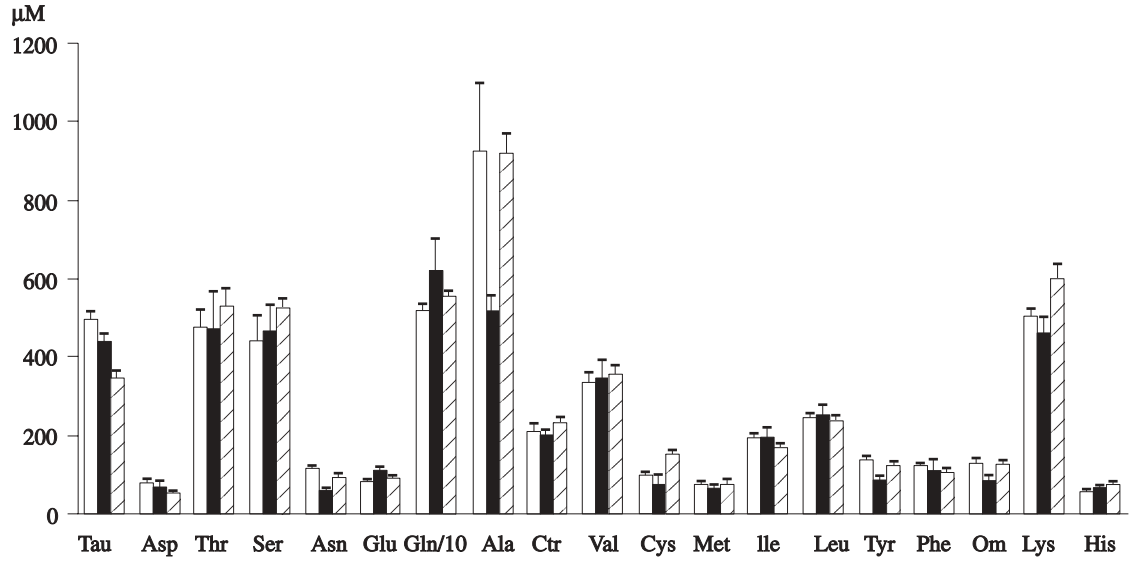

Fig. 1. Pool of free amino acids and their derivatives in the plasma from rats receiving phenobarbital and mixture of branched-chain amino acids (BCAA) and taurine. Here and in Fig. 2: Light bars: control. Dark bars: phenobarbital. Shaded bars: phenobarbital and mixture of BCAA and taurine. *+compared to the control.

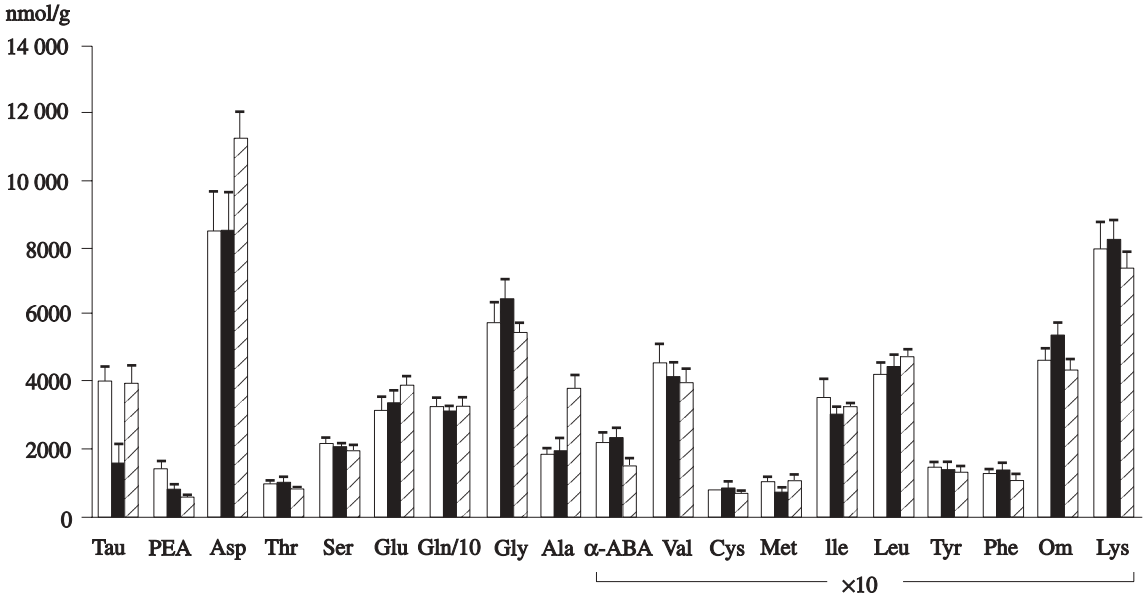

Fig. 2. Pool of free amino acids and their derivatives in the liver of rats receiving phenobarbital and mixture of branched-chain amino acids (BCAA) and taurine.

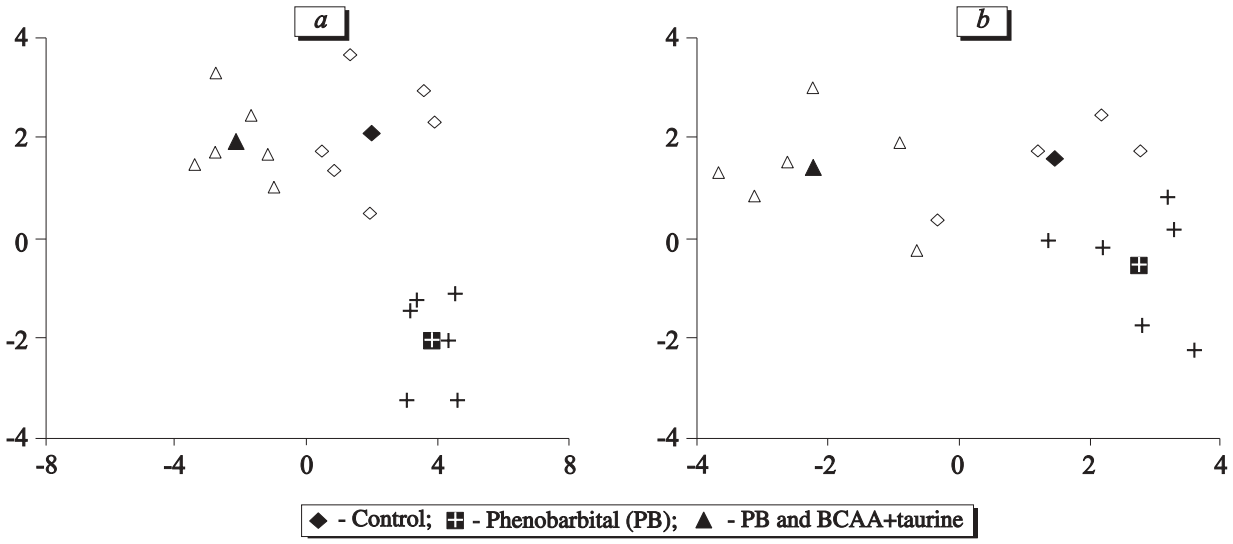

Fig. 3. Position of experimental groups on the plane of 2 major components: blood plasma (*a*) and liver (*b*).

individual samples in the plane of two major components (D^2 Mahalanobis distance) [1]. The results were analyzed 3d and 7m statistical software for medical and biological studies (BMDP Statistical Softare).

RESULTS

Plasma content of free amino acids remained practically unchanged during subchronic phenobarbital poisoning. We revealed only a decrease in the contents of asparagine and tyrosine; alanine concentration tended to decrease (Fig. 1).

The mixture of BCAA and taurine decreased the concentration of taurine in the plasma, increased the contents of cysteine and histidine, and normalized the reduced level of alanine and ornithine in rats with subchronic phenobarbital poisoning.

Phenobarbital had no effect on the content of free amino acids in the liver and blood plasma, but decreased the concentration of taurine (Fig. 2). A positive correlation was revealed between taurine concentrations in the liver and plasma. These changes reflect functional deficiency of taurine. We found a negative correlation between liver taurine content and plasma BCAA concentration in phenobarbital-treated rats (r=-0.93). The mixture of BCAA and taurine restored the relationship between these indexes.

TABLE 1. Fischer *F* Test for Experimental Treatment with BCAA-Taurine Mixture during Phenobarbital Poisoning

Blood plasma		Liver	
amino acid	F-value	amino acid	F-value
Cys	7.1136	Tau	7.7767
Tau	6.5293	PEA	4.5245
Ala	4.8966	α-ABA	3.5410
His	4.8793	Orn	3.1054
Ile	4.7375	Asp	3.0568
Orn	4.1138	Ser	2.2644
Gln	3.1183	Ala	2.1565
Leu	2.9400		

The mixture of BCAA and taurine normalized taurine content. The observed changes were accompanied by an increase in alanine concentration and decrease in phosphoethanolamine content. The content of methionine tended to decrease in rats with phenobarbital poisoning, but returned to normal after treatment with BCAA-taurine mixture. The increase in alanine concentration was previously observed in experiments with chronic administration of taurine, which illustrates stimulation of gluconeogenesis. Taurine content decreased in the plasma, but increased in the liver. These changes illustrate activation of taurine transport from the vascular bed into the liver after treatment with the preparation. Our assumption was confirmed by changes in correlation sign between taurine contents in the plasma and liver.

The concentrations of cysteine, taurine, alanine, and histidine in the plasma and contents of taurine and phosphoethanolamine in the liver were most informative (Fischer *F* test).

The mixture of BCAA and taurine most significantly normalized the content of free amino acids in the plasma. This index practically did not differ in control animals and rats with phenobarbital poisoning (Fig. 3).

Our results indicate that the mixture of BCAA and taurine normalized the reduced content of amino acids in the liver and plasma during subchronic phenobarbital poisoning.

The mixture of BCAA and taurine has a correcting effect on metabolic processes, including the con-

tent of amino acids in peripheral tissues. Our findings extend the range for application of amino acids in clinical practice.

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