Effect of Physical Training on Sulfamethazine Acetylation Rate

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We studied the rate of sulfamethazine acetylation in athletes and untrained controls aging 18-22 years. The rate of sulfamethazine acetylation in controls was characterized by a bimodal distribution: rapid and slow acetylators constituted 42 and 58%, respectively. The rate of sulfamethazine biotransformation in athletes was characterized by a trimodal distribution: ultrarapid, rapid, and slow xenobiotic acetylators constituted 48.4, 22.6, and 29%, respectively. The ultrarapid acetylation phenotype was probably associated with N-acetyltransferase induction and reflected adaptation to physical exercises.

Key Words: *athletes; acetylation phenotype; sulfamethazine; mechanisms of adaptation to physical exercises*

Long-term physical exercises cause adaptive reconstruction in various organs and systems, which provides their higher endurance to intensive muscle work. There are various methods for estimating endurance capacity [1,6]. Biochemical methods are of particular importance in this respect [2]. Excretion of acetylated metabolites is necessary for recovery after physical exercises. The rate of this process is determined by the monogenic diallel system, in which the rapid acetylation allele is dominant in relation to the slow acetylation allele. It was shown that 42 and 58% Europeans are slow and rapid acetylators, respectively.

Here we studied the effect of physical training on the rate of sulfamethazine acetylation.

MATERIALS AND METHODS

We examined 31 students (Pedagogical University, Faculty of Physical Training) aging 18-22 years and training in cross-country skiing, athletics, and other sports for 7-11 years. Control group included 12 untrained students (Technology University). The individuals had no liver, kidney, or gastrointestinal diseases and received no medications before the examination.

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The acetylation phenotype was estimated by the formation of colored drug derivatives in the reaction with chlorodinitro-substituted benzo-2,1,3-oxadiazole [3,12]. Sulfamethazine was given perorally in a single dose of 0.5 g. Urine was collected over 8 h after sulfamethazine administration. The content of sulfamethazine in urine samples taken at 1-h intervals was measured spectrophotometrically on a SF-26 spectrophotometer. Urine was diluted 1:25 with distilled water; a 10-ml aliquot was mixed with 1 ml 10% trichloroacetic acid, 1 ml 0.01 M 7-chloro-4,6-dinitrobenzofuroxan acetonitrile, and 2 ml 0.05 M acetate buffer (pH 5.5). Optical density was measured at 490 nm.

The rate of acetylation was evaluated by the ratio between the content of nonacetylated sulfamethazine to the total amount of administered drug. Kinetic curves were constructed (Fig. 1). The phenotype of acetylation was determined by estimating the sulfamethazine fraction.

The results were analyzed by Student's t test.

RESULTS

In the control group, a bimodal distribution of sulfamethazine acetylation was observed (Fig. 1), which is consistent with published data [9]. This is related to individual differences in N-acetyltransferase activity

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(sulfamethazine-acetylating enzyme), which is determined by 2 alleles in 1 locus. Previous studies demonstrated autosomal recessive inheritance of the slow acetylation phenotype. This parameter in rapid and slow acetylators is 5-8 and above 8%, respectively [4,10,11,14]. In addition, it was shown that the rate of acetylation is genetically determined (by 90%).

Phenotypes of ultrarapid, rapid, and slow acetylators were found in 15, 7, and 9 athletes, respectively (Table 1). We first demonstrated that some athletes are ultrarapid acetylators (48.4%, Table 2).

The trimodal distribution by the acetylation phenotype indicates that athletes should receive much higher daily doses of drugs, whose biotransformation in the cytosol of hepatocytes and adipocytes is catalyzed by N-acetyltransferase and proceeds via conjugation of an acetyl group to nitrogen. The contribution of genetic and environmental factors into individual variability of sulfalene pharmacokinetics was studied previously [5,10]. The contribution of genetic factors into variability of sulfalene half-life was shown to be the greatest. As differentiated from slow acetylators, in rapid acetylators these drugs even in high doses produce no side effects [3].

Intensive muscle work promotes drug absorption (due to enhanced blood circulation) [13] and elevates their maximum blood concentration [11]. Induction of N-acetyltransferase probably determines the formation of ultrarapid acetylation phenotype after long-term physical exercises. This is confirmed by the fact that subcutaneous injection of epinephrine activates N-acetyltransferase and, therefore, increases the content cAMP involved in acetylation. It was shown that catecholamine content in blood plasma increases by 15 times during intensive physical exercises [15].

The rate of biotransformation in the liver depends on the content and activity of metabolizing enzymes.

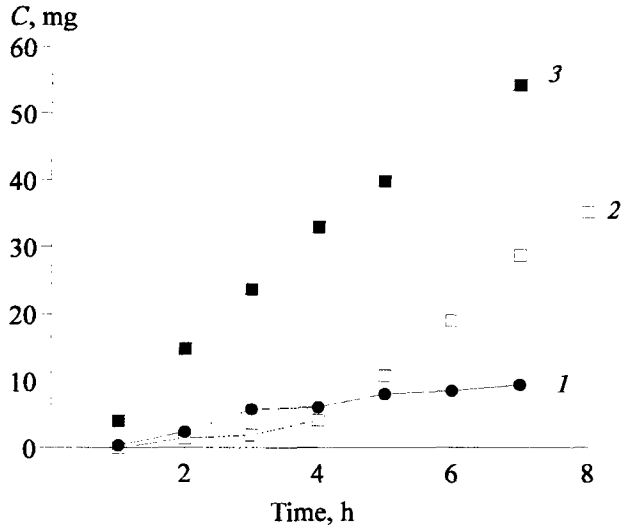

Fig. 1. Pharmacokinetics of cumulative sulfamethazine excretion (C) with urine after its peroral administration (0.5 g). Types of acetylation: ultrarapid (*1*), rapid (2), and slow (3).

Biotransformation catalyzed by N-acetyltransferase and other enzymes is under genetic control [3,5,7]. The ultrarapid acetylation phenotype in athletes suggests that regular physical training causes changes in the genotype. Previous experiments showed that decreased oxygen tension and reduced ATP and creatine phosphate contents in cultured myoblasts intensify histone acetylation and accelerate synthesis of nucleic acids and proteins [8].

The phenotype of ultrarapid acetylation formed after regular muscle training reflects adaptation of the organism. It is still unclear whether these changes in acetylation processes will be retained with the cessation of regular physical activity. The interrelation between acetylation and the type of sport also requires further investigations.

TABLE 1. Phenotype of Sulfamethazine Acetylation (Dose Fraction, %) in Athletes and Untrained Controls (*M*±*m*)

Group	Acetylation phenotype		
	ultrarapid	rapid	slow
Athletes	2.34±0.03* (15)	6.24±0.34 (7)	10.72±0.96* (9)
Controls	—	5.6±0.3 (7)	10.47±0.68* (5)

Note. Number of individuals is shown in parentheses. *p<0.001 compared to rapid acetylation.

TABLE 2. Distribution of Acetylation Phenotype in Examined Individuals (%)

Group	Acetylation phenotype		
	ultrarapid	rapid	slow
Athletes	48.4	22.6	29
Controls	—	58	42

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