# CHANGES IN RHYTHM OF LIVER ENZYME ACTIVITY IN ALBINO RATS DURING CHRONIC EXPOSURE TO VINYL ACETATE

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In experiments on male albino rats in the course of observations lasting 5 months synchronized cyclic changes in the activity of liver aspartate- and alanine-aminotransferase activity took place. Prolonged continuous exposure of the animals to vinyl-acetate vapor in a concentration of 2.4 mg/m$^3$ disturbed the rhythm of these fluctuations while maintaining the synchronization of the changes in enzyme activity. Higher concentrations of vinyl acetate (13.2 and 68 mg/m$^3$), producing chronic poisoning, led to desynchronization of the fluctuations in liver transaminase activity. The possibility of using correlation analysis for determining the degree of synchronization of the activity of enzyme systems so as to evaluate the toxic action of poisons is discussed.

KEY WORDS: vinyl acetate; alanine-aminotransferase; aspartate-aminotransferase.

The work of Sarkisov and his collaborators [4, 6] has shown that intracellular regeneration is cyclic in character and varies with the rhythm of action of external environmental factors [7, 8].

One component of the general reparative response is an adaptive change in the function of enzyme systems [3]. The development of adaptation to a chemical stimulus during an increase in the frequency of exposure to it is accompanied by intensification of protein synthesis, elevation of the partial oxygen pressure in the tissues, and an increase in the activity of the corresponding adaptive enzymes [9, 10]. Synchronization of the changes in enzyme activity plays an essential role in the development of adaptation. Under ordinary conditions of life the activity of enzyme systems is characterized by cyclic changes. A disturbance of the synchronization of these fluctuations gives rise to disharmony of metabolic processes and leads to pathological changes [7].

Maintenance or disturbance of the synchronization of fluctuations in enzyme activity during chronic exposure to a chemical stimulus must presumably lead either to the development of compensation and adaptation or to the development of toxic effects. This hypothesis was tested in a study of the liver enzyme activity in albino rats during prolonged exposure of the animals to vinyl-acetate vapor.

## EXPERIMENTAL METHOD

Male albino rats weighing 120 g, obtained from the "Rappolovo" Nursery, Academy of Medical Sciences of the USSR, were used.

The animals were divided into five groups with 10 rats in each group. The first four groups were kept under ordinary conditions: in metal chambers 0.47 m$^3$ in volume. The animals of group 1 were not exposed to vinyl acetate and acted as the control; the animals of groups 2, 3, and 4 were exposed to the prolonged action of vinyl acetate in concentrations of 2.4 ± 0.2, 13.2 ± 0.6, and 68.0 ± 2.1 mg/m$^3$, respectively. The poison was administered by a dynamic method, for 24 h daily for four months. The vinyl-acetate

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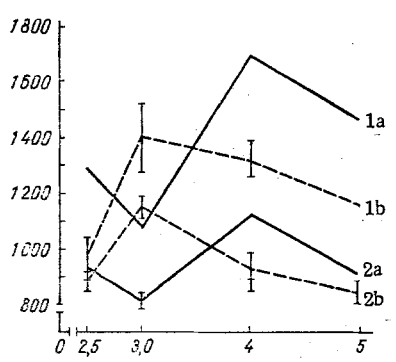


Fig. 1

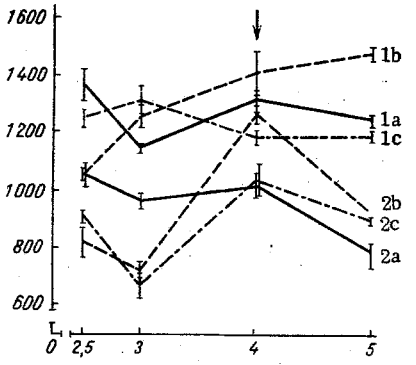


Fig. 2

Fig. 1. Dynamics of changes in alanine-aminotransferase (1) and aspartate-aminotransferase (2) activity in liver of rats under ordinary animal house conditions (continuous line) and kept in chambers (broken line). Abscissa, time from beginning of experiment (in months); ordinate, transaminase activity (conventional units/g wet weight of tissue).

Fig. 2. Dynamics of changes in alanine-aminotransferase (1) and aspartate-aminotransferase (2) activity of liver during exposure to vinyl acetate ($M \pm m$): a) 2.4 mg/m$^3$; b) 13.3 mg/m$^3$; c) 68 mg/m$^3$. Arrow marks end of exposure to vinyl acetate. Ordinate, transaminase activity (conventional units/g wet weight of tissue).

concentrations were determined by calculation and were verified by gas chromatography on the "Tsvet-4" chromatograph. The rats of group 5 were kept under ordinary animal house conditions.

Throughout the five months of observation (March-July) the activity of alanine-aminotransferase (EC 2.6.1.2) and asparate-aminotransferase (EC 2.6.1.1) in the liver was determined periodically in all the groups of rats by the method of Umbreit, Ravey, and Kingsley in Ulovich's modification [5]. The results were subjected to statistical analysis by the method of Student and Fisher. Agreement between the numerical data and the law of normal distribution was estimated by the method described by Broitman et al. [2]. To assess synchronization of the fluctuations in enzyme activity the rank correlation coefficient was calculated by Spearman's equation. The significance of the rank correlation coefficient was determined from the appropriate tables [11].

## EXPERIMENTAL RESULTS

As Fig. 1 shows, liver transaminase activity in rats kept in the animal house fluctuated during the spring and summer months. Definite synchronization was found between the waves of aspartate- and alanine-aminotransferase activity in the liver. The rank correlation coefficient was 0.87 ($P = 0.01$). This indicates a high degree of direct correlation between the fluctuations in activity of these enzymes in healthy animals.

Keeping the albino rats in an airtight chamber screened from external stimulation and providing a new environment for the animals led to changes in the cyclic fluctuations of enzyme activity and to a modification of the rhythm, but did not disturb synchronization. Direct correlation also was found under these conditions between the changes in activity of these two enzymes in the liver. The rank correlation coefficient was 0.81 ($P = 0.05$).

A similar change in the rhythm of fluctuations of enzyme activity with maintenance of synchronization occurred during exposure to vinyl acetate in a concentration of 2.4 mg/m$^3$. With this concentration the experimental animals developed adaptive changes.

The action of vinyl acetate in high concentrations led to desynchronization of the cyclic changes in enzyme activity, and this was especially marked in a concentration of 68 mg/m$^3$ (Fig. 2). Other signs of development of toxic effects also were observed in the animals in this case.

Transaminase activity is controlled by adrenocortical hormones [1] and it can be regarded to a certain degree as a nonspecific indicator of the response of the body to a chemical irritant. This suggests that the pattern of changes observed is of general importance.

Investigation of liver transaminase activity during chronic exposure to vinyl acetate thus showed that enzyme activity (at least, so far as one metabolic cycle is concerned) undergoes synchronized fluctuations. The rhythm of these fluctuations is modified during the development of adaptive changes. Synchronization of the waves of activity of the enzyme systems, however, is preserved. The action of high concentrations of vinyl acetate, causing the development of chronic poisoning, was accompanied by complete desynchronization of the waves of activity of the enzyme systems studied.

Estimation of the degree of synchronization of fluctuations in activity of enzyme systems by correlation analysis, at least within the limits of one metabolic cycle during chronic exposure to poisons, can evidently be taken as an indicator distinguishing between adaptive modifications and pathological changes.

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