# EFFECT OF ISOLATION STRESS ON THE PHARMACOKINETICS OF THE BLOOD ETHANOL IN RATS

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The rate of elimination of ethanol from the body is determined by activity of ethanol-oxidizing enzyme systems. However, the study of the rate of elimination of ethanol from the blood must include an examination of factors responsible for the induction of these systems. One such factor may be stress. It has been shown that short-term immobilization does not affect alcohol dehydrogenase activity, whereas immobilization for 14 days leads to an increase in the activity of this system [4].

Considering the facts described above, as well as the conditions of the model of experimental alcoholism used, namely keeping animals in individual cages [1], in the investigation described below the effect of isolation stress was studied on the pharmacokinetics of the blood ethanol in rats.

## EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats. In the experiments of series I 12 rats weighing 180-200 g, divided into two groups with six animals in each group, were used. The rats of group 1 were kept in a common cage for 10 days, whereas the rats of group 2 were kept in individual cages for the same period.

In the experiments of series II animals of the same groups were used; after 10 days had elapsed they were given diazepam for 3 days in a dose of 1 mg/kg twice a day intraperitoneally. The pharmacokinetics of the blood ethanol level in the rats was studied after intraperitoneal injection of alcohol in a dose of 1 g/kg in the form of a 25% solution. The ethanol concentration was determined by vapor-phase gas-chromatographic analysis [3]. The pharmacokinetic parameters were calculated by computer, using a first-order kinetics equation, allowing for absorption [2].

## EXPERIMENTAL RESULTS

The study of the kinetic curves of ethanol in animals kept in individual cages showed marked differences in its resorption and elimination (Table 1). The maximal ethanol concentration ($C_{max}$) in animals in communal cages (18.1 $\mu$mole/ml) was observed by the 15th minute, whereas in rats kept in individual cages $C_{max}$ was almost 60% lower (6.40 $\mu$mole/ml), and did not appear until after 30 min. Differences in the concentration and the time of reaching its maximum ($T_{max}$) are evidence of differences in ethanol absorption, reflected in values of the absorption constant ($K_a$). In the animals of group 1 the value of this parameter was almost three times higher than in the rats of group 2. The decrease in ethanol concentration in animals kept in individual cages was combined with an increase in the apparent distribution volume ($V_d$) of ethanol and its clearance. For instance, $V_d$ in the animals of this group was 888 mg/ml, whereas in the rats of group 1 it was 197 mg/ml. The increase in clearance, determining the volume of test tissue freed from ethanol per unit time, in animals kept in isolation was 2460 ml/kg/h compared with that in rats kept in the communal cage (1083 ml/kg/h), evidence of a marked increase in the rate of elimination of ethanol from the body. This conclusion is confirmed also by differences in the elimination constants ($K_e$). The value of this constant in rats kept in communal cages was 0.18, i.e., only half that observed in animals kept in individual cages (0.35).

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TABLE 1. Pharmacokinetic Parameters of Blood Ethanol of Rats under Different Experimental Conditions

| Group of animals | $K_e$ | $K_a$ | $T_{max}$, h | $C_{max}$, μmoles/ml | Clearance, ml/kg/h | $V_d$, mg/ml |
|---|---|---|---|---|---|---|
| 1 | 0,18 | 7,20 | 0,52 | 18,10 | 1083 | 197 |
| 2 | 0,36 | 2,60 | 0,80 | 6,40 | 2488 | 888 |
| 1 | 0,17 | 5,20 | 0,60 | 17,50 | 1100 | 202 |
| 2 | 0,23 | 4,6 | 0,76 | 7,50 | 2600 | 623 |

It can be postulated on the basis of the results of these experiments that the high rate of elimination of ethanol in animals kept in individual cages is caused by isolation stress.

To confirm this hypothesis, experiments of series II were carried out, in which the classical tranquilizer diazepam was given to animals of both groups. The results of the investigation showed that injection of diazepam into the animals considerably reduced the rate of ethanol elimination in rats kept in individual cages (by half), whereas in rats kept in a communal cage diazepam did not change the rate of ethanol elimination (Table 1).

The following conclusion can be drawn from these results: Isolation stress is one of the factors responsible for induction of ethanol-oxidizing enzyme systems. Activity of these systems, induced by isolation, evidently leads to a marked increase in the animals' ethanol consumption. Removal of stress by administration of diazepam normalizes activity of the ethanol-metabolizing systems and reduces ethanol consumption. This fact is evidence of central regulation of activity of ethanol-oxidizing enzyme systems.

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