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THE INFLUENCE OF ALIPHATIC ALCOHOLS AND THEIR HALOGEN DERIVATIVES ON THE COENZYME A IN THE LIVER OF MICE

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Abstract—The effect was studied of i.v. administration of various aliphatic alcohols such as methanol, ethanol, propanol, monochloroethanol, trichloroethanol and tribromoethanol and their corresponding aldehydes on the activity of coenzyme A in the liver of white mice. All compounds except trichloroacetaldehyde hydrate, tribromoethanol and acetone blocked the CoA. The blocking effect reached a maximum 30–120 min after the administration of the alcohols and immediately after the administration of the aldehydes. The results support the view that CoA is not blocked by the alcohols themselves but by the aldehydes, derived from the alcohols.

STUDYING the influence of ethanol on the metabolism of the brain and liver [1, 2] an inhibition of the transacetylating properties of CoA in the brain and in the liver of white mice of up to 90 per cent was observed. This inhibition is not due to the direct action of ethanol itself to CoA but is due to an action of acetaldehyde being an intermediate from ethanol-oxidation which probably forms a semimercaptide with the functional SH-group of CoA. This CoA-compound loses its transacetylating properties in the Kaplan and Lipmann test[3] (Ammon, unpublished data).

In the present paper the influence of intravenous administration of several alcohols, methanol, ethanol, propanol, 2-monochloroethanol, trichloroethanol and tribromoethanol and the corresponding aldehydes, formaldehyde, acetaldehyde, propionaldehyde, monochloroacetaldehyde, chloral hydrate, glycolaldehyde and acetone on the CoA in the liver of white mice was investigated.

The experiments were carried out not only to show whether only ethanol and acetaldehyde or other alcohols and aldehydes inhibit the CoA-activity of the liver, but also to give further evidence that the blockade of CoA is due to the aldehydes formed by the oxidation of the corresponding alcohols as in the case of ethanol.

MATERIALS AND METHODS

All experiments were performed on male NMRI mice which had free access to standard diet Altromin (Altromin GmbH Lage/Lippe) and tap water before and during the experiments and which were kept at 24° environmental temperature.

Ten μmole/g methanol; 10 μmole/g ethanol; 10 μmole/g propanol; 1·5 μmole/g formaldehyde, 4 μmole/g acetaldehyde, 5 μmole/g propionaldehyde, 12 μmole/g paraldehyde, 10 μmole/g glycolaldehyde; 80 μmole/g acetone; 40 μmole/g 2-monochloroethanol; 2 μmole/g trichloroethanol; 1·5 μmole/g tribromoethanol;

1 μmole/g 2-monochloroacetaldehyde and 4 μmole/g chloral hydrate were administered as aqueous solutions intravenously.The i.v. injections lasted 2–6 min, 30, 60 and sometimes 120 and 180 min after the administration of the alcohols and 1, 5 and 10 min—in some cases 60 and 120 min—after the injection of the aldehydes the animals were killed by immersion into liquid air. The livers were prepared while being frozen. After that the 20-fold quantity of boiling water was added and the whole kept in a boiling water bath for 3 min. After centrifugation the activity of CoA was determined in the supernantant according to the method of Kaplan and Lipmann[4] modified by Tabor *et al.*[5] This method depends on the transmission of acetate via CoA–SH on *p*-nitroaniline in the presence of ATP and glutathione by means of a transacetylating enzyme system from pigeon liver.

The values presented in the figures are means and their standard errors and are calculated from 10–15 single determinations.

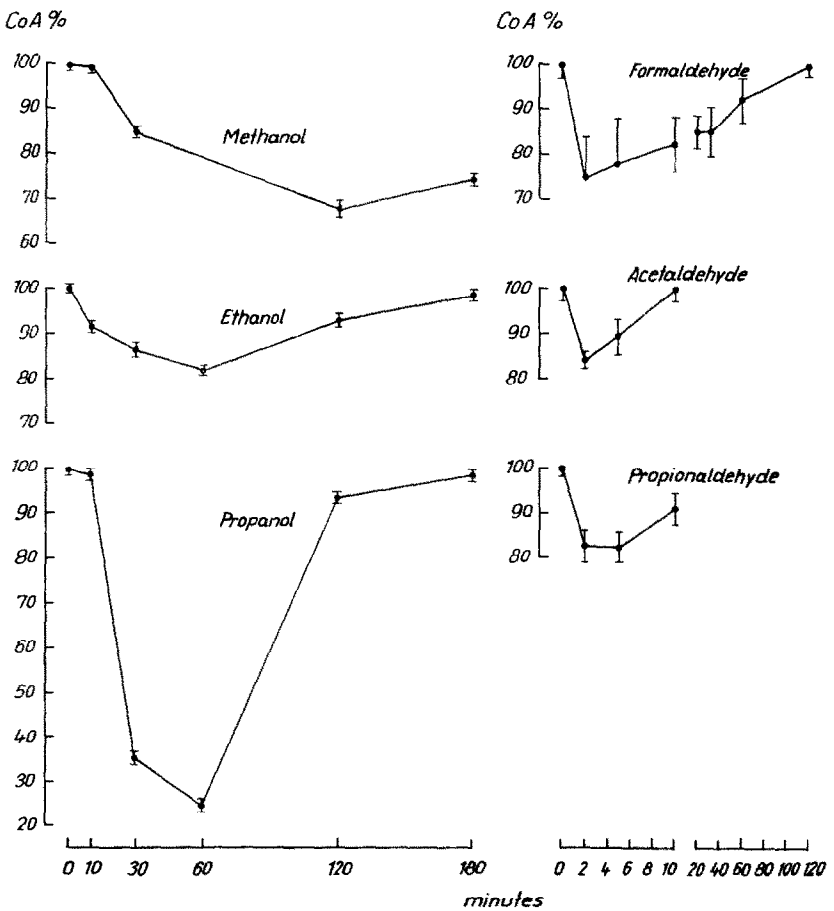

FIG. 1. Influence of i.v. administration of methanol (10 μmole/g), ethanol (10 μmole/g), propanol (10 μmole/g), formaldehyde (1·5 μmole/g), acetaldehyde (5 μmole/g) and propionaldehyde (5 μmole/g) on Coenzyme A in the liver of white mice. 100 per cent (0·319 μmole CoA/g liver) = mean value of the controls.

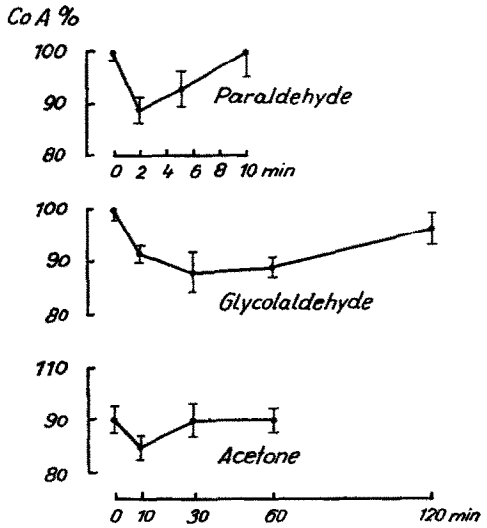

FIG. 2. Influence of i.v. administration of paraldehyde (12 μmole/g), glycolaldehyde (10 μmole/g) and acetone (80 μmole/g) on Coenzyme A in the liver of white mice. 100 per cent (0·287 μmole CoA/g liver) = mean value of the controls.

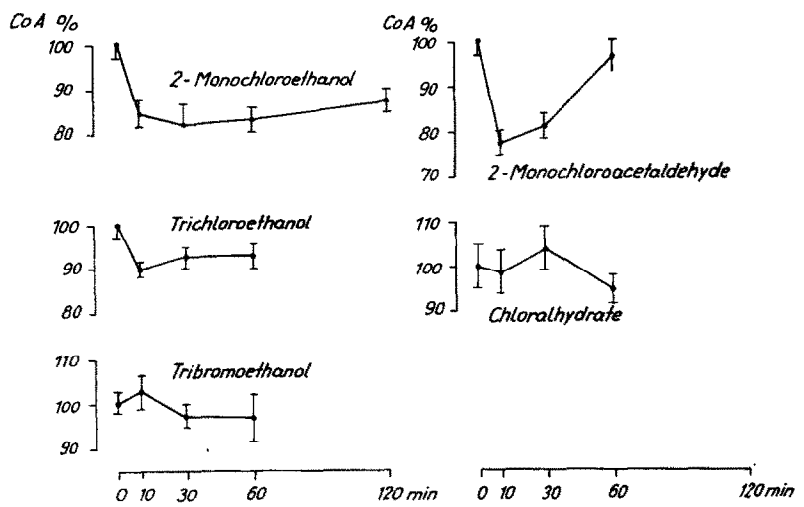

FIG. 3. Influence of i.v. administration of 2-monochlororethanol (40 μmole/g), trichloroethanol (2 μmole/g), tribromoethanol (1·5 μmole/g), 2-monochloroacetaldehyde (1 μmole/g) and chloral hydrate (4 μmole/g) on Coenzyme A in the liver of white mice. 100 per cent (0·285 μmole CoA/g liver) = mean value of the controls.

RESULTS

Alcohols

After i.v. injection of 10 μmole/g body weight of the homologous alcohols methanol, ethanol and propanol, propanol was most effective blocking CoA by 67 per cent, whereas methanol had the longest lasting effect (3 hr). Among the halogenated derivatives of ethanol monochloroethanol at a dose level of 40 μmole/g blocked CoA

to the same degree as 10 μmole/g ethanol but for twice as long. Trichloroethanol was hardly effective and tribromoethanol not at all. The smaller doses of 2 or 1·5 μmole/g respectively of the alcohols last mentioned had to be chosen since the LD_{50} of trichloroethanol and tribromoethanol are about 3 or 2 μmole/g respectively.

Aldehydes

After i.v. injection formaldehyde, acetaldehyde and propionaldehyde were considerably more toxic to white mice than the corresponding alcohols. Therefore, they had to be applied at doses of 1–5 μmole/g, that is 50–75 per cent of their LD_{50}.CoA was blocked immediately after the end of the injection of the aldehydes. The effect of propionaldhyde and acetaldehyde lasted 5 min, the effect of formaldehyde and monochloroacetaldehyde lasted 30 min, in spite of the small dose of 1 μmole/g monochloroacetaldehyde. Glycolaldehyde at a dose of 10μmole/g blocked CoA for 1 hr, trichloroacetaldehyde hydrate was ineffectual.

The effect of the different alcohols and aldehydes could not be compared at equimolar doses because their toxicity and CoA blocking activities varied.

DISCUSSION

Among the alcohols propanol caused the most powerful and methanol the longest lasting blockade of CoA in the liver. Probably methanol and monochloroethanol have less affinity with alcoholdehydrogenase than the other alcohols and hence are more slowly metabolized to their aldehydes which are the compounds that actually block CoA. The presumption that the blockade of CoA is not caused by the alcohols themselves but by the aldehydes which derive from the breakdown of the alcohols is supported by the finding that aldehydes block CoA very rapidly—the maximum blocking effect being reached after 2 min whereas the maximum blocking effect of the alcohols is observed only after 30–120 min. Furthermore, most aldehydes are more effective than the corresponding alcohols. The short duration of the effect of the aldehydes as compared to the alcohols is due to the rapid degradation of aldehydes by aldehyde-dehydrogenase and is therefore no argument against the presumption that the action of the alcohols is mediated by the aldehydes. The alcohols on the other hand behave like depots from which the active aldehydes are continuously formed by dehydrogenation at the locus of action.

The fact that trichloroacetaldehyde hydrate in contrast to the other aldehydes has no CoA blocking properties may be due to the presence of three chlorine atoms in the aldehyde molecule. For this reason the carbonyl C-atom of the aldehyde becomes strongly positive and thus favours the binding of OH-groups to the C-atom of the carbonyl group making the formation of a semimercaptide bond between the carbonyl-group of the aldehyde and the SH-group of the CoA impossible. If however a partial block of CoA can be observed after i.v. injection of trichloroethanol this may be explained by the transitory formation of nonhydrated trichloroacetaldehyde in the liver which is obviously able to block CoA before it is converted to trichloroacetaldehyde hydrate.

Tribromoethanol has no CoA blocking effect probably because it is not metabolized to the corresponding aldehyde but is conjugated with glucuronic acid and thus quantitatively excreted through the kidneys.

As shown by the blockade of CoA by glycolaldehyde the hydroxylation of the second C-atom does not influence the reaction of the aldehyde with the SH-group of CoA. On the other hand carbonyl groups alone are not able to block the prosthetic group of CoA, as is shown by the ineffectiveness of acetone.

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