Studies on the interaction between chloral hydrate and ethanol

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The synergistic actions of chloral hydrate (CH) and ethanol are well established in folk-lore but are less well substantiated pharmacologically. Both ethanol and CH are metabolized by mammalian liver alcohol dehydrogenase (EC 1.1.1.1., LAdH) (Friedman & Cooper, 1960; Sellers, Lang, Koch-Weser, Leblanc & Kalant, 1972), but the trichloroethanol (TCE) produced by reduction of CH is also hypnotic, being 1.18 times as potent as CH itself (Cabana & Gessner, 1970). In mice, CH pretreatment does not affect blood ethanol levels although acetaldehyde concentrations have been found to be increased (Greaven & Roach, 1969). Also, the conversion of CH to TCE *in vivo* appears to be increased in the presence of ethanol (Cabana & Gessner, 1970).

In order to examine more closely the metabolic interactions between CH and ethanol, their potency in producing loss of the righting reflex in mice was determined as described earlier (Taberner, Rick & Kerkut, 1972). Blood and brain levels of ethanol, TCE and CH were determined by GLC with either *n*-propanol or water as internal standard. The *in vitro* interactions between the drugs were studied using mouse LAdH and the enzyme inhibitor pyrazole (Taberner, 1974).

CH was reduced in the presence of LAdH and NADH (Km = 10 mM) and competitively inhibited the oxidation of ethanol in the presence of NAD^+ (Ki = 4 mM). Pyrazole (200 mg/kg i.p.) potentiated the effects of both CH and TCE *in vivo*, reducing the latency of action of CH but increasing the latency of TCE.

Ethanol (2 g/kg i.p.) was found to be approximately equipotent with CH (200 mg/kg i.p.), either dose individually producing loss of righting reflex lasting between 5 and 16 minutes. When given together, a marked synergism was observed: 78.5 ± 7.2 min (mean ± s.e. mean of 6 observations). The shortest latency was observed when the ethanol was given 3 min prior to the CH, although the duration was unchanged. Using the same doses given simultaneously, the ethanol produced a consistent, but not significant ($P > 0.05$) increase in brain levels of CH, but no change in the blood level. At the same time the presence of CH did not alter the brain level of ethanol, although the blood level was significantly reduced ($P < 0.05$) between 5 and 30 min of injection.

There is therefore no evidence that either CH or ethanol can affect the brain concentrations of each other. CH, by generating NAD^+ as a result of its reduction to TCE may stimulate the oxidation of ethanol by LAdH as evidenced by the fall in blood ethanol concentration observed here and the increase in acetaldehyde reported by other workers (Greaven & Roach, 1969). Conversely, the ethanol presence appears to stimulate the reduction of CH to TCE and since the latter is more potent as a hypnotic than CH the synergism observed may well be due to raised blood and brain levels of TCE.

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