Biochemical Pharmacology, Vol. 29, pp. 1445–1449.
Pergamon Press Ltd. 1980. Printed in Great Britain.

# COMMENTARY

## INTERACTIONS BETWEEN ETHANOL AND OTHER HEPATOTOXIC AGENTS

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In 1921, Hall detected the efficacy of carbon tetrachloride ($CCl_4$) in expelling hookworms from dogs [1]. In the following years, over a million humans with hookworm infestation were treated successfully with this drug [2]. Shortly after the introduction of $CCl_4$ as an anthelmintic, cases of poisoning with emesis, jaundice and other signs of liver damage occurred, and it soon became evident that $CCl_4$ was extremely toxic both for chronic alcohol addicts and for those who drank alcohol immediately before or after treatment with carbon tetrachloride [2–4]. Lamson *et al.* in 1923 [5] and Gardner *et al.* in 1925 [6] showed that simultaneous administration of ethanol with $CCl_4$ to dogs markedly increased $CCl_4$-induced liver damage and death rate. This was the beginning of the experimental research on the interrelationship between ethanol and other hepatotoxic agents.

The ability of ethanol to potentiate the hepatotoxicity of $CCl_4$ was confirmed by several investigators in dogs, rabbits, rats and mice [7–17]. Up till now no paper was published in which this effect of ethanol could not be verified.

### *Ethanol dosage*

In most of these investigations, ethanol was given prior to or together with $CCl_4$ in a single dose or in multiple doses ranging between 3.2 and 8 g/kg. These doses are higher than those commonly reached in human ethanol consumption. However, on account of a slower absorption and a faster elimination, blood ethanol levels reached in experimental animals after such doses are much smaller than those observed in humans. For example, in rats a single oral dose of 6.4 g/kg of ethanol produces maximal blood alcohol levels of 2.1 mg/ml [18], and in mice a dose of 4.8 g/kg ethanol results in maximal blood ethanol levels of 1.94 mg/ml [17]. These values are quite within the range of blood ethanol levels reported in man during drinking sprees.

In subacute experiments on rats, already a one-week exposure to 5% ethanol instead of drinking water potentiated $CCl_4$ hepatotoxicity [15]. The caloric gain from ethanol amounted to only 11.4% of total caloric intake of these rats. Thus already the moderate amounts of ethanol commonly used by many people may increase the hepatotoxicity of $CCl_4$.

### *Other hepatotoxins*

Ethanol pretreatment also enhances the hepatotoxicity of chloroform [19, 20], trichloroethane [16], trichloroethylene [9], thioacetamide [14, 17], dimethylnitrosamine [14], paracetamol [17, 21], aflatoxin $B_1$ [22] and chlorpromazin [21]. In mice, ethanol pretreatment increased the hepatotoxic effects of allyl alcohol only partially [17], whereas in the isolated perfused rat liver ethanol even prevented allyl alcohol-induced lesions [23]. Galactosamine-induced hepatotoxicity in guinea pigs was strengthened only moderately by pretreatment with ethanol [17]. Ethanol did not influence the hepatotoxicity of bromobenzene, phalloidin and praseodymium, whereas the hepatotoxic actions of $\alpha$-amanitin were attenuated after ethanol pretreatment [17]. Ethanol thus does not produce a general hypersensitivity of the liver to toxic injury but induces a specific susceptibility to only a few toxic substances.

### *Other alcohols*

Several aliphatic alcohols exert a potentiating effect on the hepatotoxicity of $CCl_4$ similar to that of ethanol [10, 24]. Methanol, 2-propanol (isopropanol), 2-butanol and 2-methylpropanol (isobutanol) are even more active potentiators than ethanol [10, 24]. In a series of alcohols administered on an equimolar basis, secondary and tertiary butyl alcohols were much more effective than normal and isobutyl alcohol [10]. The high activity of the secondary alcohols can be attributed, at least partially, to the formation of their ketone metabolites, since acetone and 2-butanone (oxidation products of isopropanol and 2-butanol, respectively) exaggerate the hepatotoxic effects of $CCl_4$ and other halogenated hydrocarbons [25–27]. Furthermore, pyrazol, by producing a decrease in the rate of acetone formation, diminishes the enhanced hepatotoxic response of $CCl_4$ to isopropanol [25]. In this respect, isopropanol and 2-butanol unequivocally differ from ethanol since acetaldehyde does not display the ability to potentiate $CCl_4$ hepatotoxicity and pyrazol does not decrease but enhances ethanol-induced potentiation of $CCl_4$ hepatotoxicity [25].

Recently, these experimental results were realized in man when employees of a drug company that packaged isopropanol were accidentally exposed to $CCl_4$ [28]. The levels of acetone in samples of expired air, and the signs of $CCl_4$ intoxication, were most



B.P. 29/11—A

severe in those employees who worked on the isopropyl alcohol line. Surely, exposure to isopropanol had exaggerated the toxic response to $CCl_4$ in this industrial outbreak.

*Mechanism(s) of action*

The early investigators presumed that ethanol enhances the toxicity of $CCl_4$ by enhancing its intestinal absorption [2]. However, ethanol potentiated $CCl_4$-induced hepatotoxicity also when $CCl_4$ was applied by inhalation [9, 10] and also in the absence of ethanol at the time of $CCl_4$ treatment [13, 14]. These experimental conditions rule out an influence of ethanol on $CCl_4$ absorption.

Potentiation of $CCl_4$ hepatotoxicity did not occur when ethanol was given only two hours before exposure to $CCl_4$ [9]. A peak potentiating response was found when the alcohol pretreatment preceded the $CCl_4$ challenge by 18 hours [24]. The existence of this latent period led to the suggestion that ethanol metabolism might be involved in the potentiation of $CCl_4$ hepatotoxicity [25]. Inhibition of ethanol metabolism by treatment with pyrazol, however, did not decrease but enhanced ethanol-induced potentiation of $CCl_4$ hepatotoxicity [25]. Furthermore, acetaldehyde, the main metabolite of ethanol, was ineffective in changing the hepatotoxic response to $CCl_4$ [14, 25]. Thus the potentiating effect of ethanol on $CCl_4$ hepatotoxicity is associated with non-metabolized ethanol.

*Microsomal mixed-function oxidase system*

Most of the hepatotoxic agents that are potentiated by ethanol are known to be metabolized in the liver to toxic metabolites, i.e. $CCl_4$ [29], trichloroethylene [30], chloroform [31, 32], thioacetamide [33], dimethylnitrosamine [34], aflatoxin [35] and paracetamol [36]. Phalloidin, $\alpha$-amanitin, praseodymium and galactosamin, on the other hand, are not subject to metabolic activation and their hepatotoxic effects were not or only moderately influenced by ethanol pretreatment [17]. These results support the hypothesis that an induction, or activation, of the hepatic microsomal drug-metabolizing system is responsible for the ethanol-induced potentiation of hepatotoxicity. In fact, acute or chronic ethanol administration produces an enhanced activity of this system *in vivo* [37–41] and *in vitro* [38, 40, 42–44]. Moreover, ethanol pretreatment was shown to enhance the *in vitro* covalent binding of $^{14}CCl_4$ and its metabolites to liver microsomal protein [13, 14], to accelerate the *in vitro* biotransformation of $^{14}CCl_4$ to $^{14}CO_2$ [13] and to increase the *in vivo* binding of $^{14}CCl_4$ to liver protein and lipid [14]. Thus an increased activation of $CCl_4$ to its toxic carbon trichloro free radical by liver microsomes seems to be induced by ethanol and to cause the enhanced $CCl_4$ hepatotoxicity.

The hypothesis is contradicted by the failure of ethanol to produce a clear-cut increment of bromobenzene hepatotoxicity [14, 17] since bromobenzene is also activated metabolically to form an epoxide [45]. The microsomal drug metabolizing system, however, is very heterogeneous, its relative activities varying with drug pretreatment [46]. To explain the specific pattern of ethanol-induced enzyme activation, the existence of a new species of cytochrome P-450 has been postulated [47, 48]. Possibly, this cytochrome P-450 may have a low affinity to an aromatic substance, thus explaining the failure of ethanol to enhance the hepatotoxicity of bromobenzene.

*Liver glutathione*

Many xenobiotics are detoxified by conjugation with glutathione (GSH) which is the first step in the formation of mercapturic acid conjugates [49]. Depletion of hepatic glutathione resulting from treatment with maleate or fasting increases the hepatotoxicity of paracetamol, 2,2-dichloroethylene, $CCl_4$, allyl alcohol and bromobenzene [50–52]. Some reduction of hepatic glutathione also occurs in acute ethanol intoxication [53, 54] and could lead to a slower detoxification and a higher activity of hepatotoxic agents. In another investigation, however, no decrease of liver GSH concentrations was found after ethanol treatment, though there was a clear-cut increase of the hepatotoxic response to $CCl_4$ and paracetamol [17]. Furthermore, thioacetamide-induced hepatotoxicity is not enhanced by hepatic glutathione depletion [52] but strongly aggravated by ethanol pretreatment [17]. A depletion of hepatic glutathione thus is not a presupposition of ethanol-induced enhancement of hepatotoxicity, though it may be implicated in the increased response to some of the hepatotoxic agents.

*Lipid peroxidation*

The peroxidation of polyunsaturated lipids in biological membranes is considered to be of basic importance for the liver injury induced by $CCl_4$ and other chlorinated hydrocarbons [29, 55]. It is a matter of debate until now, however, whether lipid peroxidation is also involved in the liver damage due to ethanol [55–60]. Lipid peroxidation after combined treatment with ethanol and $CCl_4$ was first investigated in 1975 by Maling *et al.* [14]. Ethanol pretreatment did not augment $CCl_4$-induced diene conjugation of microsomal lipids, though there was a trend towards higher values. On the other hand, combined treatment with ethanol and pyrazol, or treatment with isopropanol alone, exaggerated the peroxidative response to $CCl_4$ [14]. Lindström and Anders [61] came to a comparable result using ethane expiration of intact rats as an index of lipid peroxidation: treatment with ethanol did not influence, but isopropanol transiently increased, $CCl_4$-induced ethane production. A third group of investigators [58] found bromotrichloromethane to promote malondialdehyde production in hepatocytes from ethanol-drinking rats in a much higher degree than in cells from control animals.

Taken together, these results neither prove nor disprove the hypothesis that ethanol stimulates lipid peroxidation and by this way increases the hepatotoxic response to $CCl_4$ and to other hepatotoxic agents. It would be interesting to know, in this connection, whether inhibition of peroxidation by treatment with antioxidants can counteract ethanol in its potency to increase liver injury.

*Hepatic hypermetabolism*

Livers of rats treated with ethanol exhibit a higher rate of oxygen consumption than livers from control rats [62–66]. This hypermetabolic state is the consequence of an increased utilization of ATP by the ouabain-sensitive $Na^+$,$K^+$-activated ATPase [63] and was suggested to increase the sensitivity of the liver to hypoxia, thereby explaining the development of ethanol-induced hepatic injury [67]. In fact, rats pretreated with ethanol and exposed to reduced oxygen tension developed histological and biochemical evidence of hepatocellular necrosis, whereas control animals (also exposed to hypoxia, but not pretreated with ethanol) showed no such lesions [67].

Hypermetabolism and hypoxia may also be involved in the ethanol-induced increase of hepatotoxic injury. So it was shown that thyroid function is important for the production of toxic liver damage: hyperthyroidism increases but hypothyroidism reduces the susceptibility of the liver to $CCl_4$ [68–70]. Thyroxine also increases the susceptibility of rats to chloroform poisoning [71].

These results may be explained by differences in the hepatic oxygenation as caused by the calorigenic action of the thyroid hormones. This hypothesis is supported by the fact that hypothermia, like hypothyroidism, reduces hepatic oxygen consumption and also affords protection against $CCl_4$-induced hepatic damage [72]. Furthermore, hypoxemia induced by exposing rats to an atmosphere of 6% oxygen strongly aggravates the hepatotoxic response to $CCl_4$ [73], and hypoxemia due to carbon monoxide exposition or methemoglobinemia enhanced $CCl_4$ hepatotoxicity too [74–77].

The mechanism by which hypoxia enhances hepatotoxic injury remains unclear. One explanation is an indirect effect via depletion of adrenal hormones since adrenaline and noradrenaline also are able to enhance $CCl_4$ hepatotoxicity [78, 79]. This view is strengthened by the fact that potentiation of $CCl_4$ hepatotoxicity by carbon monoxide is dependent on the presence of the adrenal glands [74]. Hypoxia, on the other hand, may also enhance the metabolic activation of $CCl_4$ since the formation of chloroform from $CCl_4$ proceeds much faster in anaerobic suspensions of liver microsomes than in suspensions ventilated with oxygen [80].

Two experimental results, however, contradict the hypothesis that hypoxia is responsible for the interrelation between ethanol and other hepatotoxic agents. First, direct investigations of the hepatic oxygenation by hepatic vein catheterization have shown that intravenous ethanol administration does not produce a decrease but rather results in an increase in hepatic vein oxygen tension, and, furthermore, that alcoholic liver injury can develop despite unimpaired hepatic oxygenation [81]. Second, thioacetamide-induced hepatotoxicity is strongly enhanced by pretreatment with ethanol [14, 17] but diminished by exposure to an hypoxic atmosphere [73].

*Influence of previous liver injury on the hepatotoxic effects of ethanol*

There is surprisingly little information about the metabolic or structural effects of ethanol on the previously diseased liver [82]. On account of clinical observations it has been said that ethanol is harmful to patients with viral hepatitis [83, 84]. Other authors, however, did not find a relationship between drinking habits and the appearance of post-hepatic liver damage in patients with virus hepatitis [85]. Furthermore, patients with active hepatocellular injury (mostly hepatitis and cirrhosis) displayed no signs of liver injury following intravenous administration of ethanol [86]. The dose of ethanol, however, was small in these experiments (0.5 ml/kg).

In guinea-pigs pretreated with $CCl_4$, on the other hand, a single load of ethanol caused greater increments of serum enzyme activities than in control animals [87]. The smallest dose of alcohol active in this respect was 1.2 g/kg p.o. Administration of D-galactosamine, but not that of allyl alcohol, also enhanced the hepatotoxic response to ethanol [87]. These experimental results confirm the early clinical observations that ethanol is more toxic for a diseased than for a healthy liver. Thus a mutual exacerbation of hepatotoxicity may be responsible for the hepatic damage occurring after combined treatment with ethanol and other hepatotoxic agents.

*Conclusions*

The mechanisms which are responsible for the interactions between ethanol and other hepatotoxic agents are not fully elucidated and deserve further investigation. The existence of these interactions, however, is certain. But what are the consequences for man? Ethanol, of course, is the hepatotoxic agent with the highest practical importanee today. Due to the basic work of Lieber and his colleagues, it is now well established that ethanol exerts liver toxicity directly and not indirectly by dietetic imbalance [88]. A linear relationship exists between the incidence of cirrhosis in an alcoholic population and the intake of ethanol [89, 90]. The existence of considerable variations in individual susceptibility to ethanol-induced liver damage, however, is familiar to every physician [91]. These variations can be attributed to genetic and dietary factors, but may also be due to interactions with other hepatotoxic agents. The incidence of hepatotoxicity from therapeutic drugs and other xenobiotics is frequent and may be exaggerated by drinking. Thus doses of ethanol and of hepatotoxic agents that by themselves do not suffice to produce hepatotoxicity could become dangerous for the liver. This the more, as alcoholism often is accompanied by drug abuse. Interactions with other hepatotoxic agents thus should be evaluated as a possible additional factor in ethanol-induced liver damage.

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