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Journal of Hepatology 40 (2004) 198–202

Journal of Hepatology

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MILESTONES IN LIVER DISEASE

The unexpected outcomes of medical research: serendipity and the microsomal ethanol oxidizing system

Iseri OA, Lieber CS, Gottlieb LS. The ultrastructure of fatty liver induced by prolonged ethanol ingestion [Am J Pathol 1966;48:535–555]

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1. Discovery and description of a new pathway of ethanol metabolism

To settle the controversy of whether alcohol was capable of producing a fatty liver in the absence of dietary deficiencies, ethanol was incorporated in a liquid diet containing all the necessary nutrients for the rats which were given nothing else but this liquid diet and therefore had no choice but to drink the alcohol with it. Under these conditions, a fatty liver developed despite the adequate diet [1]. An ultrastructural study of these livers also revealed that the centrilobular and mid-zonal cells contained large clusters of closely packed smooth endoplasmic reticulum (SER) (Fig. 1A). This contrasted with the less abundant SER in rats fed the sucrose control diet (Fig. 1B) or a commercial Laboratory Chow (not shown). This observation was first reported in abstract form Ref. [2] and its publication [3] was soon followed by confirmation in volunteers given alcohol under controlled metabolic ward conditions [4]. In that publication, it was noted that this lesion was 'not to be considered specific for alcohol toxicity since proliferation of the SER had been seen after the administration of a number of toxic agents whose particular actions are different. This suggests that it is a common response to a range of chemical stimuli. In fact, since the enzymes which function in detoxification of some drugs have been demonstrated to reside in the SER [5], the changes observed may reflect the induction of alcohol-metabolizing enzymes'. This hypothesis of Lane and Lieber [4] was actively pursued and resulted in the discovery of a new pathway of ethanol metabolism in rodents as well as in humans. It was indeed found by Lieber and DeCarli [6] that 'the hepatic microsomes contain an ethanol-oxidizing system distinct from alcohol dehydrogenase. In vitro, it has characteristics comparable to those of microsomal drug-detoxifying enzymes and, in vivo, it is capable of adaptation to the administration of ethanol. The existence of this microsomal ethanol-oxidizing system may explain ultrastructural, pharmacological, and biochemical effects of ethanol'. This new pathway of ethanol metabolism was named the microsomal ethanol-oxidizing system (MEOS) and its chemical characteristics were described in detail [7]. In the decades to follow, this pathway was shown not only to explain the metabolic tolerance that results from chronic alcohol consumption, but also the many aspects of the associated pathology, more recently extended to the pathogenesis of non-alcoholic steatohepatitis (NASH).

It is noteworthy that, for many decades, the dogma was that alcohol dehydrogenase (ADH) was the only significant pathway for ethanol metabolism. Indeed, the multiple forms

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doi:10.1016/j.jhep.2003.12.005

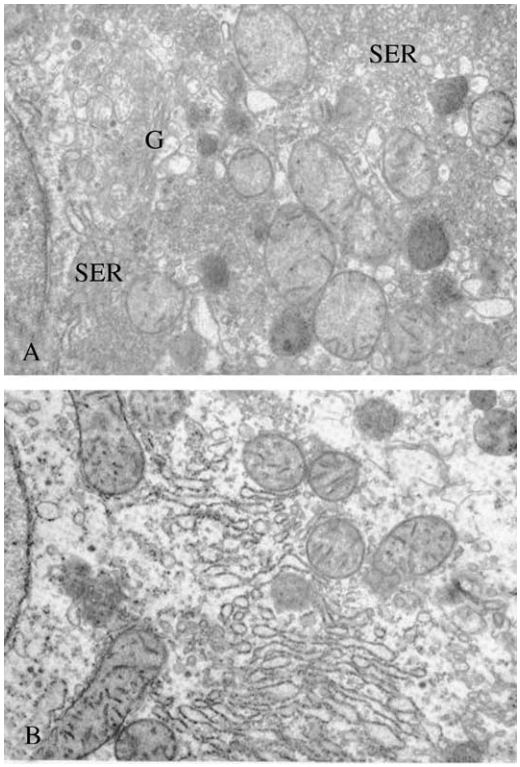

Fig. 1. (A) Portion of a hepatocyte of rat fed ethanol-containing diet for 16 days. Large clusters of smooth endoplasmic reticulum (SER) are prominent. The Golgi apparatus (G) near the nucleus has many vesicles filled with pale granules, 17 200 × [3]. (B) Rat fed sucrose control diet. Portion of a hepatocyte immediately adjacent to a central vein. It shows the usual prominent rough endoplasmic reticulum but the smooth endoplasmic reticulum is much less abundant than in Fig. 1A, 17 000 × [3].

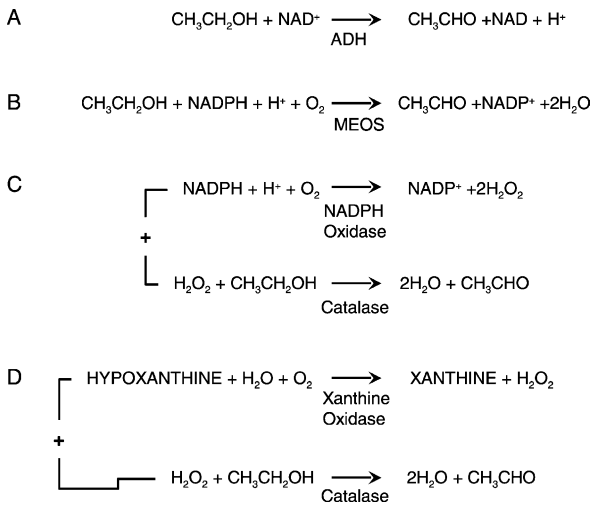

Fig. 2. Ethanol oxidation by alcohol dehydrogenase (ADH) and NAD^+ (A), hepatic microsomal ethanol-oxidizing system (MEOS) and NADPH (B), a combination of NADPH oxidase and catalase (C), and xanthine oxidase and catalase (D) [8].

of this cytosolic enzyme catalyze the conversion of ethanol to acetaldehyde, coupled with the reduction of NAD^+ to NADH (Fig. 2). This results in a strikingly altered NAD/NADH ratio and an associated redox change, shown to be responsible for many metabolic effects of ethanol [8,9]. The proposal that the new MEOS pathway plays a significant role in ethanol metabolism initiated a decade of lively debate: some invoked ADH contaminating the liver microsomes [10], whereas others adopted the prevailing view at the time, namely that this microsomal ethanol oxidation was due to a hydrogen peroxide-dependent reaction promoted by contaminating catalase [11]. Indeed, it had been postulated that the combination of H_2O_2 generation from NADPH oxidase and catalase could account for microsomal ethanol oxidation [12,13] (Fig. 2), especially because an H_2O_2-generating system (glucose–glucose oxidase) can be substituted for NADPH. Actually, the latter is not unexpected, because not only do microsomes contain catalase, but also commercial glucose oxidase (used to generate NADPH) is contaminated with catalase. It had also been reported that microsomes from acatalasemic mice fail to oxidize ethanol [14] but this claim was subsequently retracted [15]. Indeed, the catalatic activity of hepatic microsomes of acatalasemic mice subjected to heat inactivation was decreased but NADPH-dependent MEOS remained active and unaffected [16,17].

Eventually, MEOS was solubilized and separated from ADH and catalase activities by diethylaminoethyl cellulose column chromatography [18,19] as confirmed by Mezey et al. [20]. Furthermore, whereas catalase reacts peroxidatically primarily with methanol and ethanol but not with alcohols of longer aliphatic chains [21], the NADPH-dependent MEOS was found capable of metabolizing *n*-propanol as well as *n*-butanol. This was shown in hepatic microsomal preparations and in reconstituted systems that contained the microsomal components, cytochrome P-450, NADPH-cytochrome P-450 reductase and phospholipids, and exhibited no ADH or catalase activity [17–19,22,23]. Such a system was also reconstituted from acatalasemic mice [17]. Finally, successful reconstitution was accomplished with either partially purified or highly purified microsomal P-450 from alcohol [24] or phenobarbital treated [25] rats. Based on these and various other studies, and regardless of the original claim [26] to the contrary, it was finally agreed by the principal contenders involved that catalase cannot account for the microsomal ethanol oxidation [27,28], and that the MEOS is distinct from ADH and catalase and dependent on cytochrome P-450, as reviewed elsewhere [29]. This enzyme was also described in humans [30,31] and, in a new nomenclature system, it was proposed that the ethanol-inducible form be designated as CYP2E1 [32]. This CYP2E1 was found to be increased 4- to 10-fold in liver biopsies of recently drinking subjects [33], with a corresponding rise of its mRNA [34].

Despite the discovery of CYP2E1 and its prevailing role in microsomal ethanol oxidation, the term MEOS was maintained because cytochromes P-450 other than CYP2E1 (such as CYP1A2 and CYP3A4) [35] also contribute, albeit

to a lesser extent, to ethanol metabolism in the microsomes, as reviewed in Lieber [36]. Thus, the term MEOS characterizes total microsomal ethanol oxidation, not only that catalyzed by CYP2E1.

One of the most characteristic features that distinguishes CYP2E1 from the other ethanol metabolizing pathways is its remarkable inducibility, demonstrated in several species, including man (vide supra). The regulation of CYP2E1 expression is complex, involving transcriptional, posttranscriptional and posttranslational events [36].

2. Physiologic and pathologic roles of CYP2E1

CYP2E1 is highly conserved within the human population, suggesting a significant physiological function. Indeed, there appears to be a dual physiological role of CYP2E1 (Fig. 3), namely one of detoxification and other of nutritional support. That CYP2E1 contributes to the defense mechanisms of the body against the penetration of toxic xenobiotics is suggested by its location and inducibility at ports of entry into the body, and by its broad substrate specificity. Indeed, consistent with such a role is the high concentration of CYP2E1 in the nose and oropharynx (exposed to airborne xenobiotics) and in the liver, which filters all the portal circulation and traps xenobiotics entering the body through the gastrointestinal tract. The high inducibility of CYP2E1 at these sites with their adaptive response to xenobiotics is consistent with a protective role. Thus, one can speculate that CYP2E1 may have resulted from the evolutionary advantage of having a system in place that is characterized by a relative absence of specificity which allows it to presumably detoxify a variety of newly emerging xenobiotic agents.

In terms of nutritional role, CYP2E1 is inducible by fasting in the rat [37]. The increase may be due, at least in part, to ketones. Indeed, in rats [38], rabbits [39], and humans [40], acetone appears to be actively utilized, being metabolized by a microsomal acetone monooxygenase identified as CYP2E1 [41,42]. Acetone is both an inducer and a substrate of CYP2E1 [43,44]. The existence of a gluconeogenic pathway for acetone was shown by the incorporation of [^{14}C]acetone into glucose and amino acids during fasting and diabetic ketoacidosis [40,45,46]. In fact, acetone is a significant gluconeogenic precursor in fasting humans, accounting for 10% of the gluconeogenic demands, according to Reichard et al. [45].

The role of CYP2E1 in fatty acid metabolism also supports the concept of its nutritional function. Indeed, CYP2E1, in addition to its ethanol oxidizing activity, catalyzes fatty acid ω-1 and ω-2 hydroxylations [47–49].

The obese, overfed rat also exhibits substantially higher levels of CYP2E1 and total cytochrome P-450 in liver microsomes compared with non-obese animals [50], and microsomal ethanol oxidation, acetaminophen activation, and *p*-nitrophenol hydroxylation (mono-oxygenase activities

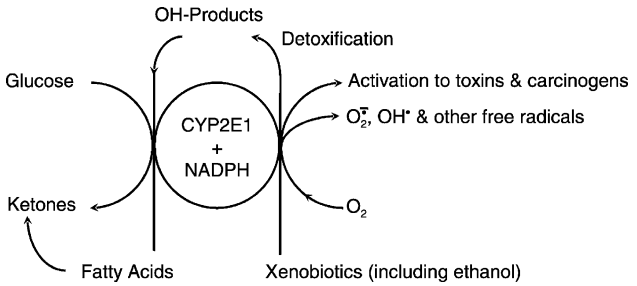

Fig. 3. Physiologic and toxic roles of CYP2E1, the main cytochrome P-450 of the microsomal ethanol oxidizing system (MEOS). Many endogenous and xenobiotic compounds, including ethanol, ketones and fatty acids, are substrates for CYP2E1 and induce its activity through various mechanisms (see text), resulting in an array of beneficial as well as harmful effects [36].

catalyzed by CYP2E1) are also enhanced [51]. This obese rat is an experimental model relevant to NASH. Indeed, the hepatopathology of NASH may be due, in part, to CYP2E1 induction. In fact, CYP2E1 is invariably elevated in the liver of patients with NASH [52] because fatty acids (which increase in obesity) and ketones (which increase in diabetes) are also substrates for CYP2E1 (vide supra and Fig. 3); their excess upregulates CYP2E1. Although the pathogenesis of non-alcoholic fatty liver disease (NAFLD), including NASH, has not yet been fully elucidated, a popular mechanism is the 'Two Hit' theory [53], the first hit being the accumulation of fatty acids in the liver by several causes (such as obesity). The second hit is the peroxidation of these fatty acids because of the oxidative stress produced by different factors, such as CYP2E1 induction [54].

Although CYP2E1 plays a useful physiologic role in ketone and fatty acid metabolism, its excess induction by overabundant substrates may also contribute to the liver pathology of NASH. This illustrates that, like with many other physiologic adaptive systems, when the adaptation becomes excessive, adverse consequences prevail. This is also illustrated by the fact that the detoxification of xenobiotics (vide supra) has, as a downside, the enhanced activation of carcinogens and the corresponding increased carcinogenicity, as reviewed elsewhere [36]. One striking example of drug toxicity is that of acetaminophen: therapeutic amounts of acetaminophen (2.5–4 g per day) can cause severe hepatic injury in alcoholics [55]. In animals given ethanol for long periods, hepatotoxic effects peak after its withdrawal [56] when ethanol is no longer competing for the microsomal pathway but levels of the toxic metabolites are at their highest. Thus, alcoholics are most vulnerable to the toxic effects of acetaminophen shortly after cessation of chronic drinking, when the induced CYP2E1 activates acetaminophen to a highly toxic metabolite. Furthermore, in terms of alcohol metabolism, there is a similar dichotomy. On the one hand, CYP2E1 leaks oxygen radicals as part of its normal operation of alcohol detoxification (Fig. 3), but when this radical production exceeds the cellular defense systems, it

results in oxidative stress with its pathologic consequences. This occurs when excess alcohol has to be metabolized. One of the consequences of this oxidative stress caused by CYP2E1 induction and associated mitochondrial injury is lipid peroxidation and membrane damage. In addition, the acetaldehyde produced by the oxidation of ethanol has abundant toxic effects. Furthermore, lipid peroxidation products such as 4-hydroxynonenal stimulate fibrogenesis which is also increased through decreased feedback inhibition of collagen synthesis because acetaldehyde forms adducts with the carboxyl-terminal propeptide of procollagen [57]. These pathophysiologic considerations are now prompting the search for CYP2E1 inhibitors effective enough, yet innocuous, to oppose the toxic effects of CYP2E1 without decreasing its physiologic functions.

3. Summary

Serendipitously, a new pathway of ethanol oxidization, namely the MEOS with its key enzyme CYP2E1, was discovered which explains the adaptive increase of alcohol metabolism upon chronic consumption. This CYP2E1 also exerts a number of important and useful physiologic functions such as xenobiotic detoxification and promotion of ketones and fatty acid metabolism. Its inducibility allows the system to adapt to various metabolic conditions but the functioning of this system is associated with the release of free radicals, the excess of which causes oxidative stress with many pathologic consequences. The challenge is now to find inhibitors that will maintain CYP2E1 activity at a useful physiological level while avoiding the toxicity of its excess functioning. Thus, the discovery of CYP2E1 provided new insights for the pathogenesis of alcoholic steatohepatitis, fibrosis, cirrhosis and non-alcoholic steatohepatitis. Thereby, it opened new prospects for improved treatment and better outcome of these deadly diseases.

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