INVITED COMMENTARY

THE ROLE OF GASTROINTESTINAL FACTORS IN ALCOHOL METABOLISM

HELMUT K. SEITZ* and GUDRUN PÖSCHL

Laboratory of Alcohol Research, Liver Disease and Nutrition and Department of Medicine, Salem Medical Centre, Zeppelinstraße 11–33, 69121 Heidelberg, Germany

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Abstract — Although the liver is the major organ responsible for ethanol metabolism, such metabolism also occurs in the gastrointestinal (GI) tract. However, compared to the liver, GI metabolism of ethanol is quantitatively much lower. Various enzyme systems have been characterized in GI mucosal cells including various isozymes of alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP 2E1) and catalase. Gastric ADH activity is one factor by which first pass metabolism (FPM) is influenced and its activity is modulated by genetics, gender, age, drugs and gastric morphology. Another important factor in FPM of ethanol is the speed of gastric emptying. In addition to mucosal ethanol metabolism, ethanol can also be oxidized by many bacterial species in the upper GI tract including oropharynx and stomach as well as in the large intestine. GI metabolism of ethanol may influence systemic bioavailability of ethanol and may lead to local toxicity most likely mediated by acetaldehyde. Such toxicity could be of importance in ethanol-associated carcinogenesis.

INTRODUCTION

Gastrointestinal (GI) metabolism of ethanol is of considerable importance, since it may affect the systemic availability of alcohol and leads to local production of acetaldehyde, possibly resulting in tissue injury. Although the presence of alcohol dehydrogenase (ADH) in the GI mucosa has been known for a long time (Pestalozzi et al., 1983), its importance became obvious only with the demonstration of the so-called first pass metabolism (FPM) of ethanol. In addition, more recently, bacterial metabolism in the GI tract has been investigated intensively and it was speculated that it contributes not only to local toxicity, but also to alcoholic liver disease and to the loss of energy observed after chronic ethanol consumption.

GI metabolism of ethanol and its role in GI pathophysiology is complex, since it is influenced by multiple factors including motility, absorption, dilution by large volumes of GI secretion and rediffusion of ethanol. This overview will focus on factors more recently investigated influencing GI metabolism of ethanol in man. Animal data will only be discussed briefly, since it seems difficult to extrapolate data collected in experimental animals to the human situation.

ETHANOL METABOLISM BY MUCOSAL ADH

In the GI mucosa, various isozymes of ADH exist (Pares and Farres, 1996; Yin et al., 1997). Class IV ADH (σ-ADH) is characteristic of the upper GI tract, class IV ADH and class I ADH (γ-ADH) coexist in the stomach, while intestinal ADH is mainly composed of class I ADH (γ-ADH). Class III ADH (ζ-ADH) is present in the mucosa of the complete GIT. σ-ADH has its highest activity in the oral and oesophageal mucosa and to a lesser degree in the stomach. It has a much higher $K_m$ of about 41 mM at pH 7.4 as compared to class I ADH with a $K_m$ of 1–2 mM for ethanol. In contrast, ζ-ADH is unsaturable.
σ-ADH is unique for the GI tract and its structure and function have been described in detail (Moreno and Pares, 1991; Pares et al., 1994; Farres et al., 1994). The quite different affinities of the three isozymes to ethanol make it extremely difficult to measure total mucosal ADH activity, since for the saturation of class III and IV ADH relatively high ethanol concentrations are needed, whereas class I ADH needs rather low concentrations and may be substrate-inhibited by higher ethanol concentrations. Thus, ethanol concentrations of 500 mM or more inhibit class I ADH, whereas ethanol concentrations below 50 mM may not completely measure σ-ADH. In many in vitro studies, 100 mM ethanol has been used to saturate class I and class IV ADH, but not class III ADH. Because of these different enzyme kinetics, it is extremely important to consider the ethanol concentrations used before drawing general conclusions.

It is also important to note that the various isozymes of ADH are capable of metabolizing other substrates, including medium and long chain alcohols, aldehydes, steroids, retinol, ω-hydroxy fatty acids and the carcinogen nitrobenzaldehyde (Pares and Farres, 1996).

GI mucosal ADH-mediated ethanol oxidation may have two important implications: firstly, gastric ethanol metabolism via ADH may contribute to gastric first pass metabolism (FPM) of ethanol and may determine the systemic availability of ethanol (Frezza et al., 1990). Secondly, mucosal ethanol metabolism via ADH, especially in the oropharynx and the esophagus (where σ-ADH activity is relatively high), may contribute to local toxicity and eventually to ethanol associated cocarcinogenesis (Seitz and Poschl, 1997).

FACTORS AND CONDITIONS INFLUENCING GASTRIC ADH ACTIVITY

Various parameters have been found to influence gastric ADH activity. These are the following.

(a) Polymorphism of the ADH 3 (class I) locus. This leads to a variability of ADH activity, since kinetic constants differ between the corresponding allelozyme<sub>11</sub> and allelozyme<sub>22</sub> (Moreno et al., 1994).

(b) A lack of σ-ADH expression. This has been observed in orientals (Baraona et al., 1991; Yin et al., 1993; Dohmen et al., 1996), and is believed to result in decreased FPM of ethanol. A lack of σ-ADH in Japanese subjects may have further importance since σ-ADH metabolizes not only ethanol but also other compounds, including nitrobenzaldehyde which is a carcinogen and needs to be detoxified by σ-ADH in the stomach (Baraona et al., 1991; Dohmen et al., 1996).

(c) Gender. It has been shown that gastric ADH activity is significantly decreased in younger women, as compared to age-matched men (Frezza et al., 1990; Seitz et al., 1993) or is not affected by gender (Moreno et al., 1994). This decreased ADH activity in gastric biopsies of women seems to be due to σ-ADH (Seitz et al., 1993).

(d) Age. Increasing age decreases gastric ADH activity. This is especially relevant for men, while in women gastric ADH activity is rather stable on a lower level over life time (Seitz et al., 1993).

(e) Ethanol concentration. Because of the various enzyme kinetics mentioned above, the concentration of alcohol consumed affects the amount metabolized. Thus, alcohol in beer (5%) undergoes less metabolism than alcohol in wine (10%) or whiskey (40%) (Roine et al., 1991, 1993). In addition, ethanol concentration also modulates the speed of gastric emptying (Holt, 1981).

(f) Drugs. Some drugs interfere with gastric ADH activity. Cimetidine is a non-competitive inhibitor of σ-ADH (Seitz et al., 1984; Caballeria et al., 1989; Seitz et al., 1992). Some inhibition of σ-ADH has also been observed with ranitidine (DiPadova, 1992) and with aspirin (Roine et al., 1990), whereas famotidin and omeprazol do not affect gastric ADH (Hernandez-Munoz et al., 1990; DiPadova, 1992).

(g) Injury. Gastric mucosal injury, including that following ethanol consumption (Seitz et al., 1993), atrophic gastritis (Pedrosa et al., 1996) and Helicobacter pylori (HP)-associated gastritis (Thuluvath et al., 1993; Osswald et al., 1994) decreases gastric ADH activity.

GASTRIC FIRST PASS METABOLISM OF ETHANOL

The differences of the areas under the ethanol concentration–time curves (AUC) obtained after oral and intravenous alcohol application have been
used to estimate FPM of ethanol. However, alcohol follows Michaelis–Menten, rather than first order, kinetics (Wagner et al., 1989) and therefore a comparison of AUCs is applicable only when blood ethanol concentrations are very low and the rate of alcohol elimination is approximately proportional to concentration. Thus, to measure FPM at higher ethanol concentrations the quantity of alcohol reaching the systemic blood orally or intravenously can be calculated by integration of the Michaelis–Menten formula over the entire blood alcohol curve (Amir et al., 1996).

It has been claimed that gastric ADH activity correlates with gastric FPM of ethanol (Frezza et al., 1990). Many of the factors mentioned above, which modulate gastric ADH activity, also modulate FPM of ethanol (chronic ethanol consumption, cimetidine, HP infection). However, there are circumstances where gastric ADH activity and FPM do not correlate. For example, patients with atrophic gastritis reveal an extremely low gastric ADH activity with no change in FPM of ethanol (Pedrosa et al., 1996). Thus, other factors besides gastric ADH activity may contribute to the FPM of ethanol. One of these factors is gastric emptying (GE) time. It has clearly been shown that delayed GE leads to an increased FPM of ethanol either due to a prolonged exposure time of alcohol to gastric ADH, to an increased hepatic FPM of ethanol or to both (Pedrosa et al., 1996). Such a delayed GE has been shown in men versus women with and without atrophic gastritis (Pedrosa et al., 1996) and in the fed versus fasted state which is associated with an increased FPM (DiPadova et al., 1987). An enhanced GE has been shown with ranitidine (Amir et al., 1996) associated with decreased FPM. Most recently, modulation of GE time by metoclopramide and scopolamine resulted respectively in an increased and a decreased FPM of ethanol without affecting gastric ADH activity (Oneta et al., 1996).

In addition to gastric FPM, hepatic FPM of ethanol may occur which may differ with the speed of intestinal absorption of ethanol (Levitt and Levitt, 1994). In the rat, the contribution of hepatic and gastric FPM of ethanol is a matter of dispute (Smith et al., 1992; Lim et al., 1993), whereas, in man, its contribution is unclear.

It has to be pointed out that FPM of ethanol exhibits a great variability between individuals, because it is influenced by so many factors. Since it seems extremely difficult to control for all these factors, the heterogeneity of the study designs in many reports may explain some of the discrepancies of the results. The contribution of the FPM of ethanol to total ethanol metabolism remains a matter of dispute, ranging between as low as 1% and as much as 20% (Frezza et al., 1990; Pares and Farres, 1996) possibly being not more than 9% (Ammon et al., 1996).

In our opinion, two factors seem to be of clinical relevance with respect to gastric ADH in man. (a) The concomitant intake of alcohol and cimetidine should be avoided, since it leads to increased blood alcohol concentrations. This is especially relevant when small amounts of ethanol are consumed repeatedly over a long period of time (Gupta et al., 1995). (b) Alcohol consumption in the elderly (frequently with atrophic gastritis) could be hazardous due to a decreased gastric ethanol metabolism (Seitz et al., 1993), an enhanced gastric mucosal susceptibility towards ethanol/acetaldehyde toxicity (Seitz and Simanski, 1994) and also a decreased water distribution space in elderly patients, which further leads to increased blood alcohol concentrations (Vestal et al., 1976).

**OESOPHAGEAL AND COLORECTAL ADH AND ITS POSSIBLE ROLE IN LOCAL ACETALDEHYDE PRODUCTION**

As already pointed out, high levels of σ-ADH exist in the oesophagus and the oropharynx (Yin et al., 1993), possibly leading to an increased ethanol metabolism and to an increased acetaldehyde concentration in these tissues. Whether this is of importance with respect to mucosal damage, mucosal regenerative changes and carcinogenesis needs further investigation. In contrast to the upper GI tract, σ-ADH is only occasionally detectable in the colorectal mucosa. Here ADH 3 polymorphism occurs. The ADH activity is comparable to that found in the stomach (Seitz et al., 1996). Rectal mucosal ADH activity measured in human biopsies is significantly higher compared to colonic ADH activity (Seitz et al., 1996). This is of interest with respect to the fact that chronic alcohol consumption results in an increased rectal cancer risk, but to a lesser extent to colonic cancer risk (Kune and Vitetta, 1992).
Most recently, a change in ADH pattern during colorectal carcinogenesis has been observed demonstrating an increased expression of δ-ADH in adenomatous polyps as compared to the adjacent normal mucosa (Egerer et al., 1997).

CYTOCHROME P450 2E1 (CYP 2E1) AND CATALASE-MEDIATED ETHANOL METABOLISM

In animal experiments, the presence of GI CYP 2E1 and its induction after chronic alcohol consumption have been demonstrated (Shimizu et al., 1990). In man, data on GI CYP 2E1 are rather limited. We succeeded recently in demonstrating the induction of CYP 2E1 in the oropharyngeal mucosa of chronic alcoholics with oropharyngeal cancer (Baumgarten et al., 1996). This induction has been shown in the normal mucosa of these patients and has not been found in control patients who were only occasional consumers of alcoholic beverages. Since CYP 2E1 is not only responsible for the metabolism of ethanol to acetaldehyde, but also the metabolism of various xenobiotics, including carcinogens such as nitrosamines, polycyclic hydrocarbons and hydrazines, such an induction could lead to an increased activation of those compounds which enter the GI tract from cigarette smoke or diets (Seitz and Osswald, 1992). A role of such induction with respect to upper GI tract cancer needs further evaluation. In addition, ethanol metabolism through CYP 2E1 also leads to free radical formation. Such free radicals could be responsible for the cocarcinogenic effect of ethanol in the oesophagus, since supplementation with the radical scavenger α-tocopherol significantly inhibited tumour formation in chemically induced oesophageal carcinoma (Eskelson et al., 1993).

Catalase activity has also been found in the gastric mucosa of rodents (Kaihovaara et al., 1996); however, no relevant data exist for man.

BACTERIAL ETHANOL METABOLISM

Experimental studies have clearly shown that gastrointestinal bacteria, including those in the oropharynx and in the stomach, are capable of metabolizing alcohol (Baraona et al., 1986) and various metabolites including different aldehydes could be detected (Levitt et al., 1982). A number of bacteria and yeasts possess ADH activity. Under anaerobic conditions these microbes are capable of producing energy through fermentation (Zeikus, 1980). Patients with tropical sprue exhibit significant endogenous ethanol levels in jejunal aspirates (Klipstein et al., 1973). A striking observation has been made in Japan where 39 cases of intragastrintestinal alcohol fermentation syndrome showed an alcohol intoxication after a carbohydrate diet in patients with GI abnormalities and associated overgrowth of Candida albicans (Kaji et al., 1984). In these patients endogenous blood alcohol levels up to 90 mg/dl have been demonstrated. It is interesting to note that alcoholics with oropharyngeal cancer frequently present with an extremely poor dental status. Oropharyngeal bacteria convert ethanol to acetaldehyde (Pikkarainen et al., 1979) and it seems possible that acetaldehyde leads to mucosal damage resulting in tissue hyper-regeneration, since we have recently demonstrated in the rat that mucosal acetaldehyde concentrations correlate significantly with mucosal cell turnover at least in the large intestine (Simanowski et al., 1994).

In the stomach under physiological conditions, bacteria are normally absent. However, in achlorhydria (e.g. medication with H2-receptor antagonists or omeprazol) and especially in atrophic gastritis, bacterial overgrowth occurs. Such bacteria also oxidize ethanol to acetaldehyde (H. K. Seitz and R. M. Russell, unpublished work).

HP also possesses ADH activity which differs from that present in the GI mucosa (Salmela et al., 1993). Since drugs which are effective in the treatment of HP-associated gastritis, such as colloidal bismuth subcitrate or omeprazol, also inhibit HP ADH activity, a possible contribution of local acetaldehyde accumulation to the development of alcoholic gastritis was suggested (Roine et al., 1992). In vivo studies in subjects who harbour HP in their stomachs have clearly shown that this bacterium by itself does not contribute to the FPM of alcohol (Osswald et al., 1994). On the contrary, because of the HP-associated gastric mucosal injury leading to a decrease of gastric mucosal ADH activity, significantly reduced FPM of alcohol was observed in the presence of HP, which increased after its eradication (Osswald et al., 1994).
More than 400 different bacterial species and $10^{14}$ individual bacteria are normally present in the human colon (Goldin, 1990). The metabolic capacity of the colonic microflora has been estimated to be at least as great as that of the liver. Many of these bacteria are capable of oxidizing alcohol to acetaldehyde and the production of acetaldehyde is therefore rather high in the colon (Jokelainen et al., 1994; Salaspuro, 1997). Data from animal studies show that more acetaldehyde per gram of tissue is present in the colon as compared to the liver (Seitz et al., 1987). Furthermore, most of this acetaldehyde is regenerated from bacteria, since germ-free animals had significantly lower mucosal acetaldehyde concentrations in the rectal mucosa as compared to conventional animals (Seitz et al., 1990). There is also some indirect evidence that acetaldehyde injures the rectal mucosa leading to secondary compensatory hyper-regeneration which makes the mucosa more susceptible to chemical carcinogens (Simanowski et al., 1986, 1994). Rectal cell turnover significantly correlates with mucosal acetaldehyde concentrations (Simanowski et al., 1994) and also with the speed of carcinogenesis in animal experiments (Seitz et al., 1990). Besides the local toxicity of acetaldehyde, which may lead to mucosal damage and to secondary compensatory hyper-regeneration (possibly involved in carcinogenesis), absorbed acetaldehyde may also contribute to alcohol-associated liver damage. Finally, the loss of energy after alcohol consumption and the so-called empty calories of alcohol could be partly explained by the metabolism of alcohol via intestinal bacteria which contribute to energy wastage (Salaspuro, 1997).

**GENERAL CONCLUSIONS**

A great number of factors influence GI metabolism of ethanol. Quantitatively, ethanol metabolism by gastric ADH, which is still relatively small as compared to that of the liver, and by gastrointestinal bacteria predominate. Gastric metabolism of ethanol is one determinant of FPM of ethanol. Since this metabolism depends in part on gastric ADH activity, which is modulated by genetics, gender, drugs, age and gastric morphology, and on the speed of gastric emptying, studies to determine FPM of ethanol must control for all these factors to avoid pitfalls and thus incorrect conclusions. Bacterial metabolism of ethanol generates sufficient acetaldehyde, possibly contributing to local mucosal injury. Although GI ethanol metabolism by CYP 2E1 is relatively small, the capacity of CYP 2E1, especially following induction after chronic ethanol ingestion, to activate procarcinogens and to generate free radicals may be of pathogenic importance.

**REFERENCES**


