Human gastric alcohol dehydrogenase activity: effect of age, sex, and alcoholism

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Abstract

As various isoenzymes of gastric alcohol dehydrogenase exist and as the effect of sex and age on these enzymes is unknown, this study measured the activity of gastric alcohol dehydrogenase at high and low ethanol concentrations in endoscopic biopsy specimens from a total of 290 patients of various ages and from 10 patients with chronic alcoholism. Gastric alcohol dehydrogenase was also detected by immunohistological tests in biopsy specimens from 40 patients by the use of a polyclonal rabbit antibody against class I alcohol dehydrogenase. A significant correlation was found between the immunohistological reaction assessed by the intensity of the colour reaction in the biopsy specimen and the activity of alcohol dehydrogenase measured at 580 mM ethanol. While alcohol dehydrogenase activity measured at 16 mM ethanol was not significantly affected by age and sex, both factors influenced alcohol dehydrogenase activity measured at 580 mM ethanol. Young women below 50 years of age had significantly lower alcohol dehydrogenase activities in the gastric corpus and antrum when compared with age matched controls (SEM) (6·4 (0·7) v 8·8 (0·6) nmol/min/mg protein; p<0·001 and 6·0 (1·3) v 9·5 (1·3) nmol/min/mg protein; p<0·001). Over 50 years of age this sex difference was no longer detectable, as high Km gastric alcohol dehydrogenase activity decreases with age only in men and not in women. In addition, extremely low alcohol dehydrogenase activities have been found in gastric biopsy specimens from young male alcoholics (2·2 (0·5) nmol/min/mg protein), which returned to normal after two to three weeks of abstinence. The activity of alcohol dehydrogenase in the human stomach measured at 580 mM ethanol is decreased in young women, in elderly men, and in the subject with alcoholism. This decrease in alcohol dehydrogenase activity may contribute to the reduced first pass metabolism of ethanol associated with raised ethanol blood concentrations seen in these people.
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Recent studies in men[1–3] and in rats[4 5] have shown that a significant fraction of ingested ethanol fails to reach the blood and that it is not retained in the gastrointestinal tract but is metabolised by first pass metabolism. The enzyme responsible for ethanol oxidation in the human stomach is alcohol dehydrogenase. Pestalozzi *et al*[6] reported the presence of a low K_m alcohol dehydrogenase in the human stomach by using immunohistology. Most recently, however, alcohol dehydrogenase isoenzymes with much lower affinity to ethanol have been detected in surgical specimens from the stomach[7 8] and in gastric biopsy specimens.[8 9] As it was reported that the activity of gastric alcohol dehydrogenase correlates with the first pass metabolism of ethanol,[10] and as the first pass metabolism was decreased in women,[10] in the alcoholic,[2] and after cimetidine treatment[11] leading to raised blood ethanol concentrations,[2 10–12] we investigated the effect of sex, age, and chronic alcohol consumption on low and high Km alcohol dehydrogenase activity in biopsy specimens from the corpus and antrum of the stomach.

Methods

PATIENTS

A total of 290 patients had gastroscopies and biopsy specimens (wet weight: 3–12 mg) were taken from apparently normal areas of the gastric corpus, or antrum, or both. Of the 290 patients, 118 were men and 172 were women with an age between 18 and 83 years. All patients required gastroscopy because of medical indications including dyspeptic symptoms and tumour exclusion. None of the patients were receiving H_2 receptor antagonist treatment. Patients with *Helicobacter pylori* infection and with moderate or severe gastritis determined by light microscopy were excluded from the study. The gastroscopy was carried out with an Olympus GIF Q endoscope and the biopsy specimen was taken by a forceps type FB3K. The study was approved by the ethics committee of the Department of Medicine, University of Heidelberg, Germany. The patients did not have any history of chronic alcohol abuse. In addition, biopsy specimens were taken from nine male alcoholics (age: 30–75 years) and from one female alcoholic (age: 45 years) at the time of hospital admission. All of these patients reported an intake of more than 100 g ethanol per day and all of them had raised serum γ-glutanyltransferase activities. In addition, all patients had histologically moderate to severe gastritis. Three of these patients had another biopsy during their stay in hospital after 14 and 19 days of abstinence from ethanol. At this time, gastric morphology returned to normal.

DETERMINATION OF ALCOHOL DEHYDROGENASE IN GASTRIC BIOPSY SPECIMENS

The biopsy specimens were frozen immediately and kept at −80°C until used. The tissue was homogenised in 100 mM glycine buffer, pH 9·6 using a specially designed homogeniser for

Eppendorf vials and finally centrifuged at 27 000 g for 15 minutes. The supernatant was used to determine alcohol dehydrogenase activity at 22°C in 100 mM glycine buffer, pH 9·6 with a final ethanol concentration of either 16 mM or 580 mM, and a nicotine adenine dinucleotide concentration of 2·6 mM. The human stomach contains three isoenzymes of alcohol dehydrogenase: The γ-alcohol dehydrogenase forms (class I) with a K_m of 1–2 mM at pH 10·0, the σ-alcohol dehydrogenase (class IV) with a K_m of 11 mM at pH 10·0, and χ-alcohol dehydrogenase (class III), which cannot be saturated with ethanol. At 16 mM ethanol γ-alcohol dehydrogenase isoenzymes are saturated, σ-alcohol dehydrogenase is partially saturated, and χ-alcohol dehydrogenase is not active. At 580 mM ethanol γ-alcohol dehydrogenase is partially inhibited by excess of substrate, σ-alcohol dehydrogenase is saturated, and χ-alcohol dehydrogenase has also a small contribution to the activity measured. The complexity of the system makes it impossible to differentiate clearly between the activities corresponding to each enzyme. Therefore, in this paper alcohol dehydrogenase activities measured at 16 mM and 580 mM ethanol are referred to activities of alcohol dehydrogenase with low or high ethanol concentrations.

The soluble protein content in the supernatant fraction was measured according to the method of Lowry *et al*[13] using bovine serum albumin as as standard.

IMMUNOHISTOLOGY OF GASTRIC ALCOHOL DEHYDROGENASE

Chemicals – protein A and sepharose CL-4B were obtained from Pharmacia Inc (Uppsala, Sweden), and horseradish peroxidase from Sigma Chemical Co (St Louis, Mo). Protein A-peroxidase was prepared as described.[14]

Immunochemicals – pyrazole sensitive human liver alcohol dehydrogenase was purified and characterised as described and used to elicit antibodies in rabbits.[15] Anti-alcohol dehydrogenase antibodies were purified by affinity chromatography: human liver alcohol dehydrogenase was immobilised on CNBr-activated sepharose CL-4B according to the method described previously.[16] A mixture of 10 ml antiserum and 10 ml of alcohol dehydrogenase-sepharose was incubated at 4°C overnight. The suspension was poured into a 0·9 cm diameter chromatography column. The gel was washed with 0·05 M phosphate buffered saline, pH 7·4, followed by 2 M sodium chloride in phosphate buffer.[17] Antibodies bound in the column were eluted with 3 M thiocyanate, pH 6, immediately dialysed against phosphate buffered saline (3×2×1), and concentrated in an Amicon ultrafiltration gel (Amicon Coop, Danvers, Mass) with PM-10 membrane to a protein concentration of 3–4 mg/ml. All elutions were carried out at a flow rate of 80 ml/h. The breakthrough fraction of the affinity chromatography column – that is, antiserum depleted of specific anti-alcohol dehydrogenase antibodies, was concentrated to the original volume and used as negative control (immunoadsorbed antiserum).

Tissue section – gastric biopsy specimens were immediately fixed in 4% phosphate buffered formaldehyde, pH 7·4, embedded in paraplast, sectioned at a thickness of 5 micron and mounted on microscopic slides. Three to five sections of each specimen were tested for the alcohol dehydrogenase content with the following immunohistochemical staining method: alcohol dehydrogenase was localised with anti-alcohol dehydrogenase antibodies. Bound antibodies were detected with a protein-A-peroxidase conjugate. The intensity of the staining was graded independently by a pathologist.

STATISTICAL ANALYSIS

Results were expressed as mean (SEM). The statistical significance of the differences in alcohol dehydrogenase activity were assessed by the Student's unpaired *t* test. p Values under 0·05 were considered to show statistical significance. The correlation between alcohol dehydrogenase activity and the intensity of the immunoreaction was analysed by the Spearman non-parametric method.

Results

In biopsy specimens from the human stomach alcohol dehydrogenase can be detected immunohistochemically in parietal and mucus producing cells and to a lesser degree in chief cells. The intensity, however, of the immunoreaction illustrated as pigment development varies interindividually (Fig 1). A significantly positive correlation was found between the intensity of the immunoreaction and the alcohol dehydrogenase activity measured with 580 mM ethanol by using the same biopsy specimen divided into two parts to perform both determinations (Fig 2).
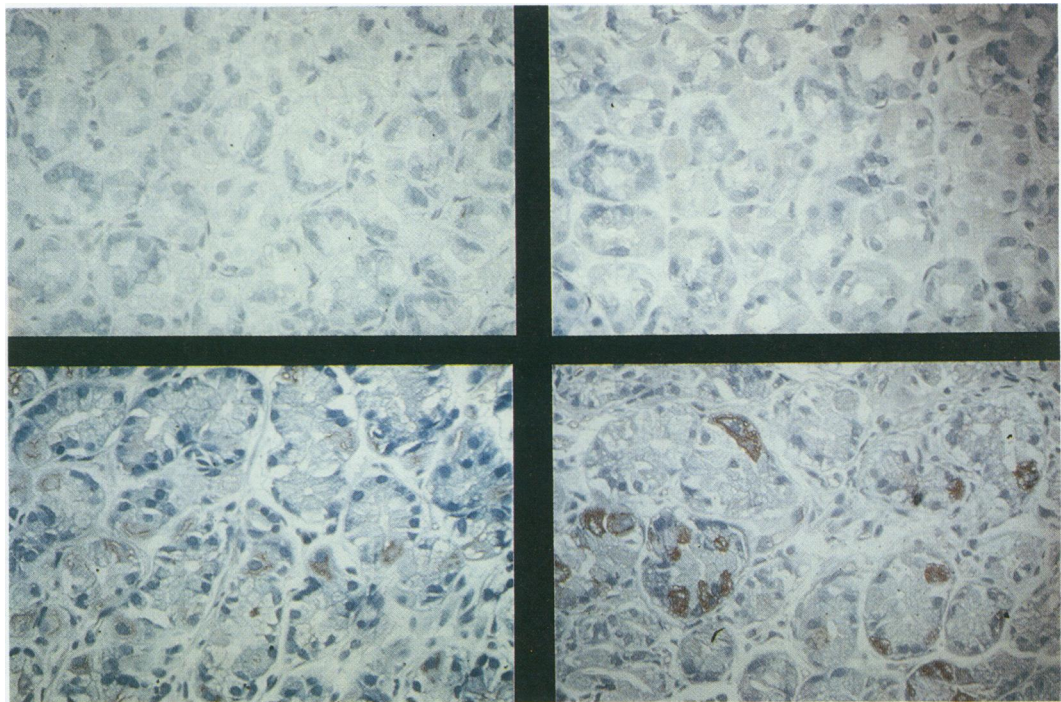
When alcohol dehydrogenase activity was measured in gastric biopsy specimens at an ethanol concentration of 580 mM no significant differences in the enzyme activity were found between the corpus and the antrum of the stomach (Table). Younger women, however, had a significantly lower alcohol dehydrogenase activity compared with age matched men, and elderly men showed a significantly lower alcohol dehydrogenase activity compared with younger men (Table). Figure 3 shows the effect of both age and sex on the activity of gastric alcohol

Effect of age and sex on gastric alcohol dehydrogenase activity

	Age 17–50 years (mmol/mg protein/min)	p Values	Age 50–85 years (nmol/mg protein/min)
Women Antrum*	6·0 (1·3)‡ (n=9) p<0·001	NS	7·1 (0·6)‡ (n=14) p<0·001
Men	9·5 (1·3) (n=11)	p<0·001	3·7 (0·4) (n=9)
Women Corpus*	6·4 (0·7)‡ (n=14) p<0·001	NS	6·2 (0·7) (n=19) p<0·001
Men	8·8 (0·6) (n=15)	p<0·001	4·7 (0·6) (n=14)
Women Corpus†	5·4 (0·8) (n=20) NS	NS	6·7 (0·8) (n=26) NS
Men	6·7 (1·3) (n=12)	NS	5·2 (0·8) (n=18)

*Alcohol dehydrogenase activity measured at 580 mM ethanol; †Alcohol dehydrogenase activity measures at 16 mM ethanol; ‡p<0·001 for the comparison with men in the same group; results expressed as mean (SEM).

Figure 1: Immunohistology of gastric alcohol dehydrogenase using a polyclonal rabbit antibody against human hepatic alcohol dehydrogenase and the PAP method. Different degrees of immunoreactivity of gastric alcohol dehydrogenase in human gastric biopsy specimens are seen: no alcohol dehydrogenase activity detactable (upper left), minimal immunoreaction (upper right), moderate immunoreaction (lower left corner), strong immunoreaction (lower right). Haematoxylin counterstain, original magnification ×100).

dehydrogenase measured at 580 mM ethanol. While the activity of the enzyme stays fairly constant during the life time in women, a sharp decrease of the activity is seen in men between the age of 40 to 50 years. This is in contrast with the alcohol dehydrogenase activity measured at 16 mM ethanol (Table). Neither age nor sex had a significant effect on this enzyme activity, although a trend towards lower activities in younger women and in elderly men can also be detected. Finally, alcoholics had a strikingly low gastric alcohol dehydrogenase activity at 580 mM ethanol compared with non-alcoholics (Fig 4). The 45 year old woman with chronic alcoholism had a gastric alcohol dehydrogenase activity of 0·7 nmol/mg protein/min. Three of the nine male alcoholics could be biopsied again during hospital stay 14 to 19 days after abstinence

from alcohol. All three showed a complete return to normal of the enzyme activity.

Discussion

The data presented show the presence of at least two types of alcohol dehydrogenase isoenzymes in endoscopic biopsy specimens from the human stomach with different activities. One isoenzyme has a low K_m for ethanol comparable with that of class I alcohol dehydrogenase isoenzymes as defined for the liver.[18] This enzyme has already been described in necropsy,[19] and in fresh surgical specimens.[7][20] By using fresh gastric mucosa, Hernandez-Munoz et al[7] found that this low K_m enzyme has an optimal pH of 10·6, is very sensitive to the inhibition by 4-methylpyrazole, and migrates cathodically on electrophoresis. This enzyme could also be detected here by immunohistology using a polyclonal rabbit antibody against human liver class I alcohol dehydrogenase. The other type of alcohol dehydrogenase has a much lower affinity to ethanol but with activities that become significant at ethanol concentrations commonly present in the human stomach after alcohol consumption.[21] It has been shown that one high K_m isoenzyme has a pH optimum of 10·5, is refractory to the inhibition by 4-methylpyrazole, and has kinetic properties corresponding to the class III (or χ-alcohol dehydrogenase) isoenzyme.[7][22] In addition, a new alcohol dehydrogenase isoenzyme, named σ-alcohol dehydrogenase has been purified from the human stomach.[9] This enzyme is a class IV isoenzyme but differs from π-alcohol dehydrogenase, has a pH optimum of 9·9, and a K_m of 41 mM at pH 7·4.[9] This gastric isoenzyme has also been detected in the rat[23] and in the baboon[24] and therefore its occurrence may be widespread in mammals. Thus, three different types of alcohol dehydrogenase isoenzymes are capable of oxidising ethanol in the mucosa of the human stomach. To measure the overall metabolism of

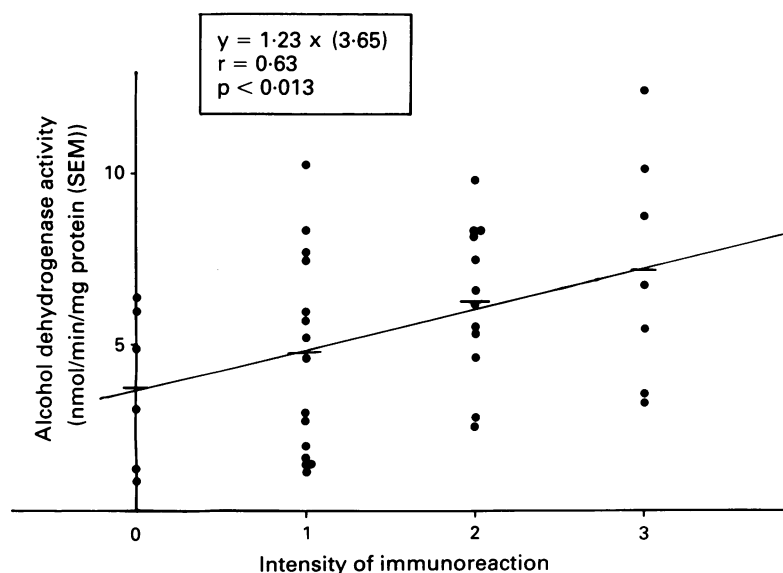y = 1·23 x (3·65)
r = 0·63
p < 0·013

Figure 2: Correlation between immunoreactivity (expressed as no=0, minimal=1, moderate=2, and strong=3 immunoreactivity) of gastric alcohol dehydrogenase and the enzyme activity measured in the same gastric biopsy specimens at 580 mM ethanol.
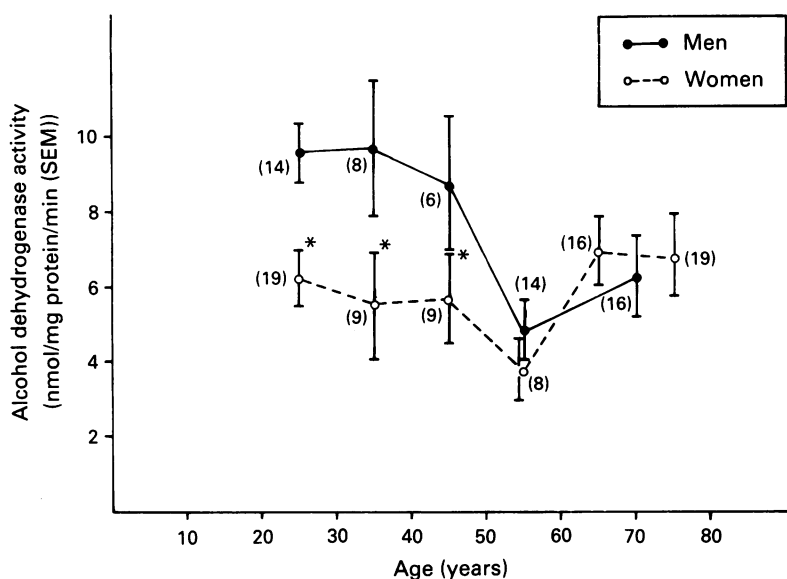
*Figure 3: Effect of age and sex on the activity of human gastric alcohol dehydrogenase measured at 580 mM ethanol. *Significantly lower (p<0·01) compared with age matched men.*

ethanol by gastric alcohol dehydrogenase and to estimate its contribution to the total alcohol oxidation in the body, sufficiently high ethanol concentrations should be used to saturate all isoenzymes.

It has to be pointed out that the specific activity of alcohol dehydrogenase measured at 580 mM ethanol is similar to that obtained by Moreno and Pares[9] and by Hernandez-Munoz et al[7] measured at 100 mM and 580 mM ethanol and is only 20–40% of that reported by Frezza et al.[10] While Frezza et al[10] concluded from their data that at least 20% of the dose of ethanol given can be metabolised by 200 g of gastric mucosa in three hours, Moreno and Pares[9] estimated that the total activity of gastric alcohol dehydrogenase measured at pH 7·5 may not exceed 1% of that of the liver and may therefore be neglegible with respect to the overall metabolism of ethanol. It seems, however, difficult to extrapolate in vivo ethanol oxidation rates from in vitro data measured in gastric biopsy specimens, as the
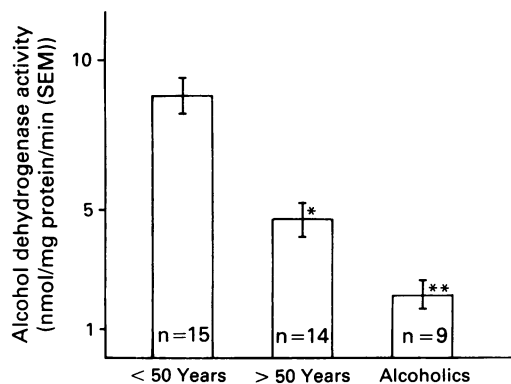

*Figure 4: Effect of chronic ethanol consumption on the activity of human gastric alcohol dehydrogenase measured at 580 mM ethanol in biopsy specimens from the corpus of male patients above and below 50 years of age. The data for non-alcoholics are those used in the table. *Significantly lower (p<0·001) compared with patients below 50 years of age. **Significantly lower (p<0·001) compared with patients above 50 years of age.*

weight of the total gastric mucosa in humans is not known. Gastric alcohol dehydrogenase may be responsible for the local production of acetaldehyde, even after a comparitively low oral intake of ethanol, and considering the toxicity of acetaldehyde, it could contribute to mucosal injury commonly seen after alcohol consumption.[25]

Various conditions have been reported under which ethanol blood concentrations increase after oral intake of ethanol including fasting,[2] chronic alcoholism,[2] cimetidine treatment,[11-13] and in women.[10] It has been suggested that the increased availability of ethanol is due to decreased first pass metabolism of alcohol in the stomach. Furthermore, as it was found that the first pass metabolism of ethanol (which is the difference between the ethanol blood concentration time curve obtained after intravenous and oral application of alcohol) correlates significantly with the activity of gastric alcohol dehydrogenase measured in endoscopic biopsy specimens, it was concluded that the increased availability of ethanol in women is due to a decreased gastric alcohol dehydrogenase activity. The data presented here confirmed the results of Frezza et al[10] and earlier results from our laboratory[26] that women exhibit a significantly lower gastric alcohol dehydrogenase activity than men when alcohol dehydrogenase is measured at high ethanol concentrations. This effect of sex, however, on gastric alcohol dehydrogenase activity is age dependent. While the activity of gastric alcohol dehydrogenase in man drops significantly during the fourth and fifth decade and becomes similar to that of women, the activity in women stays more or less constant at a lower activity level for the life time. A similar age effect as for gastric alcohol dehydrogenase has been seen for hepatic alcohol dehydrogenase.[27] Although a sex specificity of hepatic alcohol dehydrogenase distribution profile in younger age groups has been reported, this sex difference was no longer apparent after the age of 50 years.[27] It is of interest to note that neither female sex nor advanced age exhibit a significant suppressive effect on gastric alcohol dehydrogenase activity measured at low ethanol concentrations.

We have recently reported raised blood ethanol concentrations in parents after an oral intake of 0·3 g per kg body weight of ethanol compared with their children.[26] These raised ethanol blood concentrations have been attributed to a decreased distribution volume for ethanol with advanced age.[28] On the basis of the results presented here raised ethanol blood concentrations after oral alcohol administration in the elderly could be due, at least in part, to a decreased gastric first pass metabolism of alcohol by alcohol dehydrogenase.

Moreover, gastric alcohol dehydrogenase activity has been found to be extremely low in chronic alcoholics. The alcohol dehydrogenase activity was only 10–20% of that seen in sex and age matched controls. Therefore, as a result of this decreased alcohol dehydrogenase activity, first pass metabolism can be strikingly decreased in these individuals leading to raised ethanol blood concentrations as reported before.[2] It is of

interest that the gastric alcohol dehydrogenase activity in alcoholics can return to normal values during abstinence, which may be explained by a normalisation of the gastric mucosa during alcohol withdrawal.

In conclusion, the decrease of gastric alcohol dehydrogenase activity seen in women and in elderly men together with a smaller volume of distribution of ethanol in these populations may result in raised ethanol blood concentrations. Such a rise of ethanol blood concentrations may be further enhanced by chronic alcohol abuse, by fasting, or with cimetidine treatment. This should be considered in the definition of safe levels of drinking for men and women of various ages driving motor vehicles or engaging in other activities requiring a high degree of attention or co-ordination.

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