EFFECT OF CHRONIC ALCOHOL CONSUMPTION ON THE ETHANOL- AND ACETALDEHYDE-METABOLIZING SYSTEMS IN THE RAT GASTROINTESTINAL TRACT

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(Received 11 May 2001; in revised form 20 November 2001; accepted 3 December 2001)

Abstract — The activities of alcohol dehydrogenase (ADH), catalase, microsomal ethanol-oxidizing system (MEOS) and aldehyde dehydrogenase (ALDH) were measured in gastric, small intestinal, colonic and rectal mucosal samples of rats fed on a liquid alcohol diet for 1 month. In the rectum and large intestine of control animals, the activities of ADH, MEOS and catalase were maximal, whereas the activity of ALDH was minimal. After chronic alcohol intoxication, MEOS activity increased significantly in the stomach. An activation of catalase and MEOS and a decrease of the low-Km ALDH activity were observed in the rectum of experimental animals. In rats consuming the alcohol diet, hypertrophy of crypts and an increased number of mitoses were noticed in colonic and rectal mucosa. Acute alcohol intoxication (2 g/kg, intragastrically) produced significantly higher acetaldehyde concentrations in the contents of the large intestine and rectum of rats receiving alcohol chronically compared to controls. Thus, after chronic alcohol intoxication, the large intestine regions showed a greater imbalance between the activities of acetaldehyde-producing and -oxidizing enzymes, which resulted in accumulation of acetaldehyde. This mechanism can account for the local toxicity of ethanol after its chronic consumption, and relates the development of mucosal damage and compensatory hyper-regenerative processes, and possibly carcinogenesis, in the colonic and rectal mucosae of alcoholics to the effects of acetaldehyde.

INTRODUCTION

It is generally accepted that the liver is the principal site for ethanol oxidation in the mammalian body. However, it has been found that alcohol can also be oxidized in the gastrointestinal tract (GIT) and the so-called first-pass metabolism of ethanol has been demonstrated (Lamboeuf et al., 1981; Julkunen et al., 1985). Although, compared to the liver, gastrointestinal metabolism is quantitatively much lower, it is of importance, because it affects the systemic availability of alcohol and leads to the local production of toxic acetaldehyde which is possibly involved in the pathogenesis of tissue injury (Bode and Bode, 1997; Lieber, 1997; Seitz and Oneta, 1998). Earlier, it was demonstrated that, in the stomach and intestines, the reactions of ethanol and acetaldehyde catabolism were mediated by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) present in the gastric and intestinal mucosae (Lamboeuf et al., 1981). Various isozymes of ADH exist in the gastrointestinal mucosa and their distribution along the GIT is heterogeneous (Seitz and Oneta, 1998). The first-pass metabolism of ethanol has been attributed to gastric ADH activity (Lieber, 1997; Seitz and Oneta, 1998). Although some authors do emphasize that the contribution of gastric ethanol metabolism in humans is insignificant and the main site of the first-pass metabolism is the liver (Yin et al., 1997), ADH in the GIT plays a certain role in the local accumulation of acetaldehyde causing mucosal injury (Lieber, 1997). It has been found that exogenous and endogenous aldehydes interact with proteins of the gastric mucosa, and therefore the adducts formed by acetaldehyde might be a pathogenic factor in the alcoholic injury of the stomach (Salmela et al., 1997). In addition to ADH, two more ethanol-metabolizing systems, the microsomal ethanol-oxidizing system (MEOS) and catalase, can be involved in alcohol oxidation. In the rat, induction of cytochrome P450 2E1 (CYP2E1) in the upper alimentary tract squamous epithelia and in proximal colon surface epithelia has been demonstrated after chronic alcohol consumption (Shimizu et al., 1990). It was also found by Hakkak et al. (1996) that CYP2E1 was present in colonic epithelial cells, and its expression was increased by chronic alcohol intake. The CYP2E1 form has been shown to oxidize ethanol, and this process leads to free radical formation, including deleterious hydroxyl radicals, which can initiate membrane lipid peroxidation (French et al., 1993; Albano et al., 1994). In addition, CYP2E1 catalyses activation of various xenobiotics, including drugs and procarcinogens and, possibly, plays a role in carcinogenicity (Seitz and Pöschl, 1997). Catalase activity has also been found in the gastric and intestinal mucosae of humans (Beno et al., 1994), mice (Cai and Wei, 1996) and rats (Salmela et al., 1996). It has been demonstrated that in addition to ADH, catalase may play a significant role in gastric ethanol metabolism in rats (Salmela et al., 1996). Bacterial metabolism of ethanol in the colon has been investigated intensively in recent years and it has been speculated that it contributes not only to local toxicity, but also to alcoholic liver disease (Seitz et al., 1990; Salaspuro, 1997).

Prospective studies have shown increased incidence of rectal cancer in subjects consuming alcohol regularly (Kune and Vittita, 1992; Seitz and Pöschl, 1997). The accumulation of acetaldehyde in the colon during ethanol metabolism has been suggested to be at least partly responsible for colorectal cancer associated with alcohol consumption (Seitz et al., 1990; Simanowski et al., 1994). However, no comprehensive studies have been done on enzymes producing acetaldehyde nor ALDH in the rectum of the rat. In the present study, we examined the effect of chronic alcohol consumption on the activities of ADH, MEOS, catalase and ALDH in the mucosa of different...
regions of the GIT with a view to estimating the possible contribution of the ethanol- and acetaldehyde-metabolizing systems to the local accumulation of acetaldehyde and toxic ethanol effects in the GIT.

MATERIALS AND METHODS

Treatment of the animals and their diet

Male Wistar rats with an initial body weight of 150–180 g consumed a liquid isocaloric alcohol and control diet for 1 month. During the first 3 days the amount of ethanol in the diet was 2.8% and from the fourth day to the 35th day it was 3.5%. The diet was nutritionally adequate and contained (as calories) 17.8% of protein, 21% of fat, 35.4% of carbohydrate (or 60.9% for controls), 25% of ethanol (for the experimental group) and 0.4% of minerals and vitamins. This percentage of alcohol in the diet was used according to the recommendations of Derr et al. (1988) to avoid malnutrition in experimental animals. The control animals consumed the liquid diet in which ethanol was replaced by an isocaloric amount of sucrose. The diet was prepared every day from 106 g of skimmed milk powder, 53 g of whole milk powder ‘Malutka’ (both purchased from Bellakt, Volkovysk, Belarus), 27 g of sucrose (or 90 g for controls), 5 g of cellulose powder; 840 ml of water, 47 ml of 96% ethanol (for the experimental group) and 10 g of rape oil. The diet intake was recorded daily, whereas the weight gain was monitored twice a week. For ethanol determination in the animals fed the alcohol-containing diet, blood samples (50 μl) were taken from the tip of the tail on three occasions at different times. Blood ethanol was analysed by head-space gas chromatography (Pronko et al., 1993).

The daily dietary intake of control and alcohol diets was approximately the same (455.6 ± 11.7 and 424.1 ± 12.9 g/kg body weight/day, respectively), as well as the weight gain during the 30-day treatment. In the control group, body weight increased from 173.9 ± 2.5 to 243.8 ± 5.8 g and in the experimental group the increase was from 174.5 ± 2.6 to 232.0 ± 4.3 g. The consumption of ethanol per day fluctuated from 10 to 14.5 g/kg body weight, with a mean of 11.4 g/kg body weight per day during the treatment period. The experimental animals were found to be ethanol-intoxicated, the extent of the intoxication being similar to that after administration of a low or moderate dose of alcohol and the diurnal blood-ethanol levels fluctuated from 2.2 to 16.7 mM (10–77 mg/dl). The following mean blood-ethanol concentrations (± SEM) were found: at 09:00, 11.3 ± 4.6 mM; at 15:00, 2.3 ± 0.5 mM; and at 21:00, 5.9 ± 3.0 mM.

One month after the start of the experiment, the group of rats receiving the ethanol diet (n = 9) and that receiving the control diet (n = 9) were given a 2 g/kg body weight dose of ethanol intragastrically. One hour later, the rat abdominal cavities were opened under hexenal anaesthesia (90 mg/kg, intraperitoneally), and samples of the contents of the stomach, small intestine, colon and rectum were collected and immediately frozen in liquid nitrogen. The samples were homogenized with 4 volumes of 0.6 M perchloric acid and 0.5 mM thiourea solution at 0–4°C and the supernatants after centrifugation were used for ethanol and acetaldehyde determination by gas chromatography as described earlier (Pronko et al., 1993).

Assay of enzyme activities

For enzyme activity determination, the rats were decapitated after overnight starvation. Their peritoneal cavity was opened and the stomach, small and large intestines (caecum, colon and rectum) were removed. The samples were washed in a cooled isotonic sodium chloride solution, dried with filter paper and the mucosal layer was separated with a scalpel. Subsequently, the mucosa was either used for isolation of fractions or frozen in liquid nitrogen in which the samples were stored until examination. ADH dehydrogenase activity was assayed in the post-mitochondrial supernatant (20 000 g, 1 h) in 100 mM glycine buffer (pH 9.6) containing 1 mM NAD and 25 mM of ethanol. NADH formation was measured spectrophotometrically at 340 nm at 25°C, by the method of Koivistio and Salaspuro (1996). Reductase activity of ADH was determined in 100 mM phosphate buffer (pH 6.4) containing 1 mM of NADH and 5 mM acetaldehyde at 25°C, by measuring the decrease of NADH. The microsomal fraction was isolated according to Stohs et al. (1976). MEOS activity was determined by the method of the set (1979). The peroxisome-enriched λ-fraction was isolated by the method of Antonenkov et al. (1982). The peroxidatic activity of catalase was determined in 0.1 M phosphate buffer (pH 7.4) containing peroxisomal protein, 15 mM semicarbazide–HCl and 50 mM ethanol at 37°C. After 10 min of preincubation the reaction was initiated by addition of 10 mM H2O2 and stopped after 10 min by addition of 2 ml 0.6 M perchloric acid. The acetaldehyde formed was determined gas chromatographically (Pronko et al., 1993). ALDH activity was assayed spectrophotometrically (Lamboeuf et al., 1981; Koivistio and Salaspuro, 1996) with 5 mM and 100 μM acetaldehyde as substrates at 37°C. Protein was determined according to the method of Lowry et al. (1951).

Histological study

For histological studies, samples of the oesophagus, fundus and pyloric regions of the stomach, the jejunum, the transverse colon, the caecum and the rectum from control and experimental group animals were fixed in a 10% neutral formalin, dehydrated in alcohol, cleared in xylene and mounted in paraffin wax. Sections 7 μm thick were stained with haematoxylin and eosin and mounted on polystyrene. The histological preparations were examined using a light microscope.

Statistical analysis

The results are expressed as means ± SEM. Unpaired Student’s t-test was used to determine the significance of the differences between the means of the values obtained from the experimental groups and those obtained from the control groups.

RESULTS

ADH dehydrogenase and reductase activities

The distribution of ADH activity both with ethanol and acetaldehyde as substrates was heterogeneous in different GIT regions of control rats (Table 1). The lowest dehydrogenase as well as reductase ADH activities were observed in the mucosa of the small intestines, and the highest ones were in the rectal
The dehydrogenase activity of ADH in the rectum was significantly higher than that in the stomach, small intestines and colon. The reductase activity of ADH in the small intestines and colonic mucosa was significantly lower in comparison with rectum. However, the stomach and the rectum did not differ significantly in ADH activity with acetaldehyde as substrate. Chronic alcohol intoxication had no effects on ADH activity (Table 1).

**MEOS and catalase activities**

MEOS activity in the stomach of control rats was significantly higher than that in the small intestines (Table 2) and activity in the rectum was significantly higher compared to that in the small intestines and the colon. Chronic alcohol treatment produced a significant increase of MEOS activity in the stomach. In the rectum of the experimental animals, the MEOS activity was 149% higher than that in the controls, but this increase was not statistically significant. The peroxidatic activity of catalase in rats on the control liquid diet ranged in the following order of increasing levels: stomach, small intestines, rectum, colon (Table 2). This activity was significantly higher in the colon compared to the stomach. The consumption of the alcohol diet led to significant activation of catalase only in the rectum (Table 2).

**ALDH activity**

The pattern of distribution of ALDH activity in the mucosa of the GIT of control rats was different from that observed for ethanol-metabolizing enzymes. The activity of ALDH with low $K_M$ was the highest in the small intestines (Table 3). In the colon and rectum, activity of this isoform of the enzyme was significantly lower than that of the stomach and the small intestines. The absolute values of low-$K_M$ ALDH activity in the colon were 30-fold lower and in the rectum 11-fold lower, compared to that in the small intestine. The high-$K_M$ ALDH activity was almost 10-fold lower in the colonic and rectal mucosa, compared to the stomach and the small intestinal mucosa (Table 3), and the differences were highly significant.

### Table 1. Effect of chronic alcohol consumption on alcohol dehydrogenase (ADH) activity in rat gastrointestinal tract (GIT) mucosa

<table>
<thead>
<tr>
<th>GIT regions</th>
<th>Control diet</th>
<th>Ethanol diet</th>
<th>Control diet</th>
<th>Ethanol diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>4.66 ± 0.84</td>
<td>4.95 ± 0.87</td>
<td>44.87 ± 2.76</td>
<td>44.70 ± 2.38</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1.28 ± 0.22*</td>
<td>1.17 ± 0.12*</td>
<td>15.54 ± 1.44**</td>
<td>16.44 ± 1.87**</td>
</tr>
<tr>
<td>Colon</td>
<td>5.71 ± 0.41††</td>
<td>5.82 ± 0.74††</td>
<td>26.25 ± 3.04**</td>
<td>21.16 ± 1.54**</td>
</tr>
<tr>
<td>Rectum</td>
<td>12.56 ± 0.55***††‡‡</td>
<td>12.77 ± 0.95***††‡‡</td>
<td>58.67 ± 7.05***††‡‡</td>
<td>52.26 ± 2.24***††‡‡</td>
</tr>
</tbody>
</table>

Values are means ± SEM for six rats per group. Student’s $t$-test: *$P < 0.01$, **$P < 0.001$ versus stomach; †$P < 0.01$, ††$P < 0.001$ versus small intestine; ‡$P < 0.001$ versus colon.

### Table 2. Effect of chronic alcohol consumption on the microsomal ethanol-oxidizing system (MEOS) and peroxidatic catalase activities in rat gastrointestinal tract (GIT) mucosa

<table>
<thead>
<tr>
<th>GIT regions</th>
<th>MEOS (nmol NADPH formed/min/mg of protein)</th>
<th>Catalase (nmol acetaldehyde formed/min/mg of protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1.82 ± 0.31</td>
<td>7.92 ± 7.00</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.75 ± 0.24*</td>
<td>18.06 ± 5.40</td>
</tr>
<tr>
<td>Colon</td>
<td>1.03 ± 0.15*</td>
<td>31.38 ± 9.23*</td>
</tr>
<tr>
<td>Rectum</td>
<td>2.61 ± 0.48††‡</td>
<td>23.57 ± 8.0</td>
</tr>
</tbody>
</table>

Values are means ± SEM for six rats. Student's $t$-test: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus stomach; †$P < 0.05$, ††$P < 0.01$ versus small intestine; ‡$P < 0.05$ versus colon; ‡‡$P < 0.05$ versus control diet.

### Table 3. Effect of chronic alcohol consumption on aldehyde dehydrogenase (ALDH) activity in rat gastrointestinal tract (GIT) mucosa

<table>
<thead>
<tr>
<th>GIT regions</th>
<th>ALDH low $K_M$ (nmol NADH formed/min/mg of protein)</th>
<th>ALDH high $K_M$ (nmol NADH formed/min/mg of protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1.00 ± 0.30</td>
<td>4.20 ± 0.60</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3.40 ± 0.50**</td>
<td>6.3 ± 0.60</td>
</tr>
<tr>
<td>Colon</td>
<td>0.11 ± 0.07††</td>
<td>0.52 ± 0.14***††</td>
</tr>
</tbody>
</table>

The low- and high-$K_M$ ALDH activities were obtained using acetaldehyde as substrate at 100 μM and 5 mM concentrations, respectively. Values are means ± SEM for six rats. Student’s $t$-test: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus stomach; †$P < 0.001$ versus small intestine; ‡$P < 0.05$ versus control diet.
The lowest activity of ALDH with high $K_m$ was determined in the rectum. After a month of ethanol consumption, the activity of ALDH with low $K_m$ significantly decreased only in the rectal mucosa (Table 3).

Acetaldehyde concentration

The assay for the acetaldehyde content in different GIT regions 1 h after acute ethanol administration showed that high acetaldehyde levels were in the stomach and small intestine of rats, but no significant differences were found between the control and experimental animal groups. At the same time the colonic and rectal acetaldehyde concentrations were higher in rats subjected to chronic alcohol intoxication, in comparison with control animals. The results in Table 4 also show that tissue-acetaldehyde concentrations in the GIT after acute ethanol loading did not differ significantly between control and chronic ethanol-treated rats.

Histology

The results of the histological studies of the GIT organs in animals fed on the liquid alcohol diet showed some structural changes. Thickening of the stratified squamous epithelium covering the oesophagus and glandular portion of the stomach was revealed in chronically intoxicated rats. We found hyper trophy of the stomach fundus and body mucosa, hypertrophy of the gastric fundic glands accompanied by an enlargement of their sizes and a dilatation of the base regions, as compared with the controls. A dilatation of the blood vessels and focal leukocytic infiltration were detected in the mucosa. At the same time, no ulcers, erosions or any other defects of the gastric mucosa were seen. The jejunum showed moderate crypt hypertrophy and enhancement of the mitotic activity in their epithelium. The colon transversum, and especially the rectum, demonstrated hypertrophy of crypts, an increased number of mitoses in the mid-third of the intestinal glands and moderate dilatation of the mucosal blood vessels.

DISCUSSION

The results of this study show that the activities of ethanol-metabolizing enzymes and their response to chronic alcohol intoxication were distinct in different portions of the rat GIT. Thus, relatively high ADH activity was determined in the stomach and the colon and the highest was in the rectum of animals of all the groups. For determination of ADH activity, we used ethanol at 25 mM concentration. Taking into account that small and large intestinal ADH is essentially composed of class I ADH (Seitz and Oneta, 1998), the enzyme is saturated during the essay procedure in these sections of the GIT. In the stomach, where class IV and I isozymes of ADH are present, total ADH activity may be partly underestimated in the determination procedure.

The reductase activity of ADH in the GIT of control and alcohol-treated animals, as well as the dehydrogenase activity of the enzyme, ranged in the following decreasing order: rectum, stomach, colon and small intestine. The ADH reductase activity was 5–10-fold higher than the ADH dehydrogenase activity (Table 1). This is in agreement with the established fact that ADH is much better suited for aldehyde reduction, especially at neutral pH. At maximal velocity, the rate of acetaldehyde reduction is ~40-fold greater than the rate of alcohol oxidation for the enzyme from human liver (Pietruszko, 1979). The activities of rat liver ADH isoenzymes determined with acetaldehyde as a substrate were several-fold higher compared to the activities determined with ethanol (Mezey and Potter, 1983). The Michaelis–Menten constants for ethanol were 3.3–8.6-fold higher than that for acetaldehyde for different isoenzymes of the enzyme studied (Mezey and Potter, 1983).

The relatively high dehydrogenase activity of ADH in the rectum (2.6-fold higher compared to the stomach and 2.2-fold higher compared to the colon) can cause an increase in the level of acetaldehyde after alcohol treatment and may play a role in ethanol-dependent injury of the rectal mucosa. Besides, it should be taken into consideration that ADH of bacteria inhabiting the large intestine of humans and rats can also oxidize ethanol, causing production of high concentrations of reactive and toxic acetaldehyde (Seitz et al., 1990; Jokelainen et al., 1996, 1997). In the control rats, the activity of MEOS was significantly higher in rectal mucosa, compared to the small intestines and colon. MEOS activity levels in the small intestine (0.75 ± 0.24 nmol of acetaldehyde/min/mg) were close to those determined by the authors of the method (Seitz et al., 1979) (0.407 ± 0.058 nmol of acetaldehyde/min/mg). However, Seitz et al. (1982) found lower MEOS activity in the colon, compared to values reported in the present work for rectal mucosa. Partly it may be explained by the fact that the MEOS activity in the

Table 4. Effect of acute alcohol intoxication on ethanol and acetaldehyde concentrations in the contents of different gastrointestinal tract (GIT) regions of rats consuming ethanol chronically

<table>
<thead>
<tr>
<th>GIT regions</th>
<th>Acetaldehyde (µmol/g)</th>
<th>Ethanol (mmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control diet</td>
<td>Ethanol diet</td>
</tr>
<tr>
<td>Stomach</td>
<td>64.74 ± 14.45</td>
<td>60.54 ± 12.39</td>
</tr>
<tr>
<td>Small intestine</td>
<td>98.22 ± 16.25</td>
<td>118.2 ± 10.24</td>
</tr>
<tr>
<td>Colon</td>
<td>7.93 ± 1.22</td>
<td>18.50 ± 3.94*</td>
</tr>
<tr>
<td>Rectum</td>
<td>18.09 ± 3.95</td>
<td>30.50 ± 7.13</td>
</tr>
</tbody>
</table>

Ethanol (2 g/kg, i.g.) was administered to control and 1-month ethanol-fed rats, and ethanol and acetaldehyde concentrations were determined in samples of gastric and intestinal contents 1 h after acute ethanol administration. Student’s t-test: *P < 0.05 compared with the control group.
rectum was 2.5-fold higher compared to the colon (Table 2). After consumption of the alcohol diet, we observed a statistically significant increase in MEOS activity only in the stomach. This is in line with the information that chronic ethanol consumption causes an induction of cytochrome P450 2E1 in the mucosa of the upper GIT regions of rats (Shimizu et al., 1990) and that such treatment has no effect on colonic MEOS activity (Seitz et al., 1982). We found that MEOS activity in the small intestine of rats consuming ethanol diet was 25% higher, compared to rats on the control diet, but the difference was not statistically significant. Earlier, an increase in ethanol oxidation by small intestinal microsomes (Seitz et al., 1979) and an induction of CYP2E1 in rat colon after alcohol feeding (Hakkak et al., 1996) were reported. The adequate carbohydrate content of the liquid alcohol diet used in our experiment (35%) possibly explains this discrepancy. It is known that high induction of the MEOS and hepatic microsomal CYP2E1 by ethanol can be achieved with a low carbohydrate (Teschke et al., 1981) or carbohydrate-deficient (2.5%) diet (Korouian et al., 1999). MEOS activity in the GIT, including rectum, possibly contributes to ethanol oxidation in order to produce acetaldehyde and free radicals playing an important role in the pathogenesis of various alcoholic injuries (French et al., 1993; Albano et al., 1994).

It should be noted that there are no literature data on alcohol metabolism by the peroxidatic reaction of catalase in the mucosa of the GIT. Previously some authors observed only catalase activity of this enzyme by measuring the decrease in hydrogen peroxide during the reaction (Beno et al., 1994; Salmela et al., 1996). The latter authors, determining catalase activity in vitro, concluded that rat catalase, in addition to ADH, may play a significant role in gastric ethanol metabolism. As our studies showed, the peroxidatic activity of catalase was higher in the rectum of rats consuming the control diet. An exogenous supply of ethanol with the liquid diet activated the catalase peroxidatic reaction in the rectum and possibly increased its contribution to alcohol metabolism.

The histochemical studies of Chieco et al. (1998) have shown that activity of ALDH with acetaldehyde as substrate in mM concentrations is much lower in the large intestine than in the stomach and small intestine. According to the data of Koivisto and Salaspuro (1996) the high $K_m$ ALDH activity was significantly lower in the colon than in the upper parts of the GIT. Our results expand these data, as we have found relatively low ALDH activity both in the rectal mucosa and in the colon at both μM and mM concentrations of acetaldehyde.

It is of interest that, in the rectum, low ALDH activity is associated with the highest activity of ADH and catalase, as compared with other regions of the GIT. In our experiment, chronic alcohol consumption produced a significant decrease of low $K_m$ ALDH activity and in addition an activation of catalase and MEOS in the rectum of rats. The low-activity ALDH cannot possibly compensate for acetaldehyde production by relatively high ADH, peroxidatic catalase and MEOS activities in the mucosa of large intestine, and this may contribute to local acetaldehyde accumulation in the large intestine of alcohol-treated animals equally with acetaldehyde produced by intestinal microflora. This assumption is supported by our data: acute alcohol intoxication produced significantly higher acetaldehyde concentrations in the contents of the colon and rectum of rats receiving alcohol chronically, as compared to the controls. We did not measure the acetaldehyde concentrations in the mucosa of the various gastrointestinal segments. However, it was demonstrated that the concentration of acetaldehyde in rat colonic mucosa was higher than that in liver and blood after an acute dose of ethanol. The acetaldehyde levels were significantly higher in the rectum compared to the caecum; chronic ethanol consumption, however, did not influence them (Seitz et al., 1990).

Our data obtained in the rat could be extrapolated to the human situation with limitations, since ADH isoenzymes differ between rodents and man. However, some features of the distribution of activities of alcohol- and aldehyde-metabolizing enzymes along the GIT, as well as the morphological changes observed in the GIT after ethanol consumption, are very similar in rat and man. We observed significantly higher ADH activity in rat rectal mucosa, compared to colon. The same correlation of ADH activities in colon and rectum has been described for humans (Seitz et al., 1996). In the rat, ALDH activities of colonic mucosa were lower when compared with the liver and stomach (Koivisto and Salaspuro, 1996). We found that low- and high-$K_m$ ALDH activities in rat colon and rectum were significantly lower, compared to those in the stomach and small intestine. The above data are in good agreement with the information that the overall ALDH activity of human rectal mucosa was considerably lower than that reported for liver (Agarwal et al., 1997). These findings are of interest with respect to the fact that heavy drinking results in an increased rectal cancer risk, but to a lesser extent colon cancer risk (Kune and Vettila, 1992).

It is known that alcohol misuse by humans contributes to the development of cancers of the oropharynx, oesophagus, liver and rectum (Shimizu et al., 1990; Maier et al., 1994a; Seitz et al., 1998). Ethanol itself is not a carcinogen, but, under certain experimental conditions, it acts as a co-carcinogen and a tumour promoter (Seitz et al., 1998). At the same time, its metabolite acetaldehyde is regarded as a mutagen and a carcinogen capable of damaging DNA molecules (Fang and Vaca, 1995). Our morphological studies on chronically intoxicated rats produced findings similar to those previously observed in rats (Simanowski et al., 1993, 1994; Maier et al., 1994b). The data from the rat model confirm previous findings in humans. Thus, chronic alcohol misuse in heavy drinkers leads to rectal mucosal hyperproliferation (Simanowski et al., 2001). These morphologic changes are possibly related to an increased production of reactive and toxic acetaldehyde, which may lead to mucosal damage and to secondary compensatory hyperregeneration (Seitz et al., 1990). This suggestion is supported by the fact that acetaldehyde intake with drinking water also produced hyperplastic and hyperproliferative changes in the upper regions of the GIT (Cai and Wei, 1996; Homann et al., 1997).

Thus, in the rat the unfavourable correlation between the relatively high activities of acetaldehyde-producing enzymes and relatively low activities of acetaldehyde-oxidizing enzymes in the large intestinal regions is aggravated after chronic alcohol consumption. The decreased activity of low-$K_m$ ALDH in alcohol-fed animals associated with increased or unaltered activities of ADH, catalase and MEOS in the mucosa of the colon and especially of the rectum results in an imbalance between the production and disposition of acetaldehyde. The latter causes elevated levels of acetaldehyde in the lumen of the rat colon and rectum.
these portions of the intestine after chronic alcohol consumption. This mechanism can account for the local toxicity of ethanol when consumed chronically and relates the development of mucosal damage and compensatory hyper-regeneration processes (possibly involved in carcinogenesis) in colonic and rectal mucosa to the effect of acetaldehyde.

Acknowledgements — This work was supported by a grant from the Fundamental Research Foundation in Belarus (B97-389). We thank Ms Lyudmila Kiryukhina for her help in the preparation of the English version of the manuscript.

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