PAPERS

Prostaglandin E₂ and prostaglandin F_{2α} biosynthesis in human gastric mucosa: effect of chronic alcohol misuse

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Abstract

Background and Aims—The results of experimental studies support the hypothesis that decreased prostaglandin production might play a part in the gastric mucosal injury induced by alcohol. In this study, it was investigated whether alcohol misuse impairs the synthesis of prostaglandin E₂ (PGE₂) and prostaglandin F_{2α} (PGF_{2α}) in gastric mucosa.

Patients—Fifty six alcoholic patients and 66 subjects without alcohol misuse were included in the study.

Methods—Mucosal biopsy specimens were obtained from the antrum and body of the stomach. Maximal synthesis rates of PGE₂ and PGF_{2α} were determined in the microsomal fraction of the biopsy specimens.

Results—The rates of synthesis of both prostaglandins in biopsy specimens from the antrum were not significantly different from those obtained in the body. Synthesis of both prostaglandins was significantly reduced in alcoholic patients who abstained less than five days compared with the non-alcoholic group with normal mucosa (PGE₂–40%, PGF_{2α}–42% respectively). In non-alcoholic patients with severe gastritis PGE₂ synthesis was increased (+30%, *p*<0.05) and PGF_{2α} synthesis was decreased (–42.5%, *p*<0.025). In alcoholic patients with severe gastritis PGE₂ synthesis was depressed by almost 60% (*p*<0.001) compared with the non-alcoholic group with severe gastritis. Neither colonisation of *Helicobacter pylori* nor smoking had a significant influence on the prostaglandin synthesis.

Conclusions—Chronic alcohol misuse is associated with significantly reduced capacity for prostaglandin synthesis in gastric mucosa and this alcohol induced decrease in prostaglandin synthesis is modulated by the presence and degree of gastritis.

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Keywords: alcohol misuse, gastric mucosa, gastritis, *Helicobacter pylori*, prostaglandins E₂ and F_{2α}, stomach.

Alcohol is the most widely used and misused drug, the acute and chronic ingestion of which

was shown to lead to distinct functional disturbances and mucosal injury in the stomach of both animals and humans.^{1,2} Ethanol at concentrations of 5%–10% and more, disrupts the mucosal barrier^{1,3} and causes focal areas of pronounced mucosal hyperaemia, oedema, epithelial necrosis, and mucosal haemorrhage.^{1,4,5} The mechanism by which alcohol leads to gastric mucosal injury has not yet been clarified.

Endogenous prostaglandins, especially PGE₂ and PGI₂, are assumed to be of importance in maintaining the normal function and structure of the gastric mucosa.^{6,7} Exogenous PGE₂ and its derivatives have been shown to protect the gastric mucosa against various noxious agents.^{6,8} The results of experimental studies support the hypothesis that decreased prostaglandin production might play a part in the mucosal injury induced by alcohol.^{9,10} It has recently been reported that the acute ingestion of alcohol, at a concentration comparable to that of wine, significantly reduces the PGE₂ output in gastric juice in healthy subjects.¹¹

This study was performed to clarify the question whether or not prostaglandin synthesis is impaired in gastric mucosa of patients with chronic alcohol misuse. Because gastritis might influence prostaglandin synthesis, the synthesis of PGE₂ and PGF_{2α} was studied in gastric biopsy specimens of alcoholic patients and in non-alcoholic controls with normal gastric mucosa and mild or severe gastritis.

Smoking has been shown to influence prostaglandin metabolism in the mucosa of the stomach.^{12,13} Because smoking is often associated with alcohol misuse, the effect of smoking on prostaglandin synthesis was evaluated separately.

Methods

PATIENTS

One hundred and twenty two patients in whom an upper gastrointestinal diagnostic endoscopy was performed were included in the study. In all cases, the examination was carried out to investigate upper abdominal complaints, such as bloating, or pain, or heartburn. Fifty six were alcohol misusers and had been consuming an average daily amount of alcohol in

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excess of 60 g for more than two years. In 46 of these patients the period of abstinence before the endoscopy was less than one week. On histological examination 17 had normal gastric mucosa, 19 had mild gastritis, and 10 had severe gastritis in accordance with the classification proposed by Wyatt and Dixon.¹⁴ In these patients the gastroscopy was performed within five days after the last alcohol intake. In addition, another group of 10 alcoholic patients who had been abstinent for at least 12 days before endoscopy were studied (six patients with normal mucosa and four patients with mild gastritis on histology). Sixty six patients with no history of alcohol misuse (mean alcohol consumption <20 g/day) served as controls (non-alcoholic group). Eleven of these had a normal gastric mucosa, 38 had mild gastritis, and 17 had severe gastritis on histology. Criteria for exclusion from the study were: use of non-steroidal anti-inflammatory drugs, glucocorticoids, antacids or carbonic anhydrase blockers within the last two weeks. Patients with cirrhosis or gastric or duodenal ulcer were also excluded from the study. Table I summarises the data on the distribution of age, sex, smoking, and the presence of *Helicobacter pylori*.

The study was approved by the ethics committee of the Robert-Bosch-Hospital, and all the patients gave their informed consent.

BIOPSY SPECIMENS

The endoscopy was performed by two experienced gastroenterologists who together decided where in the stomach the biopsy specimens should be obtained from. In addition to tissue from the antrum, corpus, and fundus taken for routine histology and a rapid urease test, three specimens were obtained from the antrum 3–4 cm from the pyloric ring (mean (SD)) fresh weight 14.6 (6.3) mg for measurement of prostaglandin formation. To be able to compare prostaglandin synthesis in different parts of the stomach, additional biopsy specimens were taken from the upper part of the body of the stomach in 10 non-alcoholic patients (seven with normal gastric mucosa, three with mild gastritis).

STUDY DESIGN

Specimens for histology were fixed in formalin buffered saline and embedded in paraffin wax,

and 5 mm sections were prepared for light microscopy in the standard manner. Sections were stained for *H. pylori* with haematoxylin and eosin or cresyl violet.¹⁵ In addition, *H. pylori* colonisation was determined by a gel based rapid urease test (CLO-test, ASTRA Chemicals GmbH, Wedel). A positive result was indicated by a colour change at four hours.

Biopsy specimens taken for measurement of prostaglandin synthesis were immediately transferred to an ice cold 1.15% solution of KCl. Microsomes were prepared within 90 minutes, and then suspended in 200 ml Krebs-Ringer-HEPES buffer, pH 7.4 (100 mM NaCl, 4.78 mM KCl, 1.15 mM K₂HPO₄, 8.8 mM HEPES).¹⁰ Incubation, prostaglandin extraction and estimation of PGE₂ and PGF_{2α} were performed as described earlier.¹⁰ Briefly, to achieve optimal synthesis of prostaglandins, glutathione (5 mM), haemin (1 mM), MgSO₄ (3 mM) and CaCl₂ (5 mM) were added to the incubation medium.

After preincubation at 37°C for three minutes, the reaction was started by the addition of 50 ml arachidonic acid (100 mg/ml) and stopped after 0 (blank value), 2.5, or five minutes by adding 50 ml acetylsalicylic acid (10 mM) and immediately heating in a boiling water bath for five minutes. The assay of prostaglandin synthesis was linear between 0 and five minutes. All tests were done in duplicate. The PGE₂ and PGF_{2α} contents of the samples were determined by radioimmunoassay as described recently.¹¹ The recovery rate of PGE₂ was 85%–95% and that of PGF_{2α} was 95%–100%; the intra-assay variations were 3.5% and 5.4% respectively.¹¹ The DNA content of samples of the homogenates was determined by the method of Fiszer-Szafarz *et al.*¹⁶ Determination of DNA was chosen as the reference variable so as to avoid such confounding factors as variations in the amounts of mucus and fluid adhering to the biopsy specimens.

STATISTICS

Group results are expressed as means (SEM). For between group comparisons the unpaired *t* test or its non-parametric analogue, the Wilcoxon two sample test, were used.

Results

PROSTAGLANDIN SYNTHESIS

Antrum versus body

Comparison of the rates of prostaglandin synthesis between biopsy specimens from the antrum and those from the corpus in 10 patients disclosed no significant differences: PGE₂ 97 (14) v 101 (17) and PGF_{2α} 42.1 (16) v 39 (14) pg/mg DNA × min respectively.

Non-alcoholic patients with and without gastritis

In patients with mild gastritis the PGE₂ synthesis did not differ significantly from that in non-alcoholic group with normal gastric mucosa (92 (13) and 105.5 (17) pg/mg

TABLE I Patient characteristics and *H. pylori* colonisation of alcohol misusers and controls without alcohol misuse

	Non-alcoholic group	Alcohol misusers Duration of abstinence	
		<5 days	>12 days
Patients (n)	66	46	10
Male:female	36:30	20:16	8:2
Mean age (y)	55 (15)*	52 (13)*	48 (6)*
Smokers (%)	18.2	50	70
<i>H. pylori</i> colonisation (%)	56	52.2	40
Histology: normal mucosa (n)*	11 (4)	17 (4)	6 (2)
Mild gastritis (n)*	38 (18)	19 (13)	4 (2)
Severe gastritis (n)*	17 (15)	10 (7)	

*Number of patients *H. pylori* positive are given in parentheses.

Figure 1: Influence of chronic alcohol misuse (alcohol) on gastric mucosal PGE₂ synthesis in patients with normal mucosa (normal), mild gastritis, and severe gastritis. Values are means (SEM). No alcohol=patients not misusing alcohol.

DNA×min respectively), whereas in non-alcoholic group with severe gastritis, PGE₂ synthesis was greatly increased (137 (24), pg/mg DNA×min, $p<0.05$; Fig 1). Synthesis of PGF_{2α} in non-alcoholic patients with mild gastritis was decreased by 23% compared with non-alcoholic patients with normal mucosa (33 (4.0) and 43.5 (6.5) pg/mg DNA×min respectively, $p<0.05$). The reduction of PGF_{2α} synthesis was more pronounced in non-alcoholic patients with severe gastritis (25 (5) pg/mg DNA×min, $p<0.025$; Fig 2).

Alcoholic patients with and without gastritis

The synthesis of PGE₂ was clearly reduced (~40%) in the alcoholic patients with normal mucosa who continued to drink within five days of their endoscopy compared with the non-alcoholic group with normal mucosa (Fig 1, $p<0.05$). In alcoholic patients with mild gastritis, PGE₂ synthesis was not significantly decreased compared with the corresponding non-alcoholic group (Fig 1, $p>0.05$). However, in alcoholic patients with severe gastritis, PGE₂ synthesis was depressed by almost 60% (49 (22) pg/mg DNA×min) compared with the non-alcoholic patients with severe gastritis (137 (24) pg/mg DNA×min; $p<0.001$).

In the subgroups with normal mucosa, synthesis of PGF_{2α} was significantly reduced in the alcoholic patients who continued to drink to within five days of their endoscopy compared with the non-alcoholic patients (Fig 2, $p<0.025$). Although PGF_{2α} synthesis was not influenced by the degree of mucosal inflammation in the alcoholic patients (Fig 2), in the group of alcoholic patients with mild gastritis PGF_{2α} synthesis was still significantly lower than in the corresponding control group ($p<0.025$).

Figure 2: Influence of chronic alcohol misuse (alcohol) on gastric mucosal PGF_{2α} synthesis in patients with normal mucosa (normal), mild gastritis, and severe gastritis. Values are means (SEM). No alcohol=patients not misusing alcohol.

Effect of alcohol abstinence

In the group of alcoholic patients who abstained from alcohol for more than 12 days, PGE₂ synthesis exhibited almost normal values (93.5 (27) pg/mg DNA×min) whereas PGF_{2α} synthesis was still diminished (28.5 (19; $p<0.05$).

Effect of H pylori colonisation

A comparison of the non-alcoholic group negative for *H pylori* with those colonised with the organism disclosed that the rates of synthesis of PGE₂ and PGF_{2α} were not different (Table II). In the *H pylori* positive group of alcoholic patients PGE₂ synthesis was slightly reduced compared with the *H pylori* negative group ($p>0.05$), whereas PGF_{2α} values did not differ (Table II). Colonisation of *H pylori* had no significant influence on the prostaglandin synthesis in either subgroup of patients with normal mucosa or mild gastritis (data not shown).

Effects of smoking

The mean values of PGE₂ synthesis were slightly lower in smokers, both in the non-alcoholic group and the group of alcoholic patients, but the differences were not significant ($p>0.05$; Table III). An investigation of the

TABLE II Effect of *H pylori* colonisation on prostaglandin synthesis in antral mucosa

	<i>H pylori</i>	<i>n</i>	PGE ₂	PGF _{2α}
Non-alcoholic group	Negative	29	98.4 (14.4)	39.7 (8.3)
	Positive	37	103.7 (18.1)	31.6 (6.5)
Alcohol misusers	Negative	22	71.8 (21)	24.2 (7.4)
	Positive	24	55.6 (24)	22.4 (5.3)

Values for PGE₂ and PGF_{2α} are pg/μg DNA×min (mean (SEM)).

TABLE III Effect of smoking on prostaglandin synthesis in antral mucosa

Patients	Smoking	n	PGE ₂	PGF _{2α}
Non-alcoholic patients	no	54	108.1 (21)*	33.2 (7.2)
	yes	12	95.2 (19.2)	29.1 (6.7)
Alcoholic patients	no	23	67.6 (22.3)	22.6 (5.9)
	yes	23	59.6 (24)	24.3 (7.1)

Values for PGE₂ and PGF_{2α} are pg prostaglandin/μg DNA×min (mean (SEM)).

influence of smoking on PGE₂ synthesis in the subgroups with and without gastritis also failed to disclose any significant differences. This applied in particular to the subgroups with severe gastritis (Fig 1), although the number of cases were few (smokers in the non-alcoholic group three of 17, in the alcoholic patients four of 10). The synthesis of PGF_{2α} was not influenced by smoking (Table III).

Discussion

For the purpose of studying factors that might affect prostaglandin metabolism in the human stomach, different approaches have been used. Determination of prostaglandin content in mucosal biopsy specimens,⁶ and the measurement of the production of prostaglandins from endogenous or exogenous prostaglandin precursors (in particular arachidonic acid) in mucosal biopsy specimens^{17–18} have both been applied. Each of these methods has its own particular problems with respect to the interpretation of the data obtained. A major disadvantage of using whole mucosal biopsy specimens or homogenates of mucosal biopsy specimens is the pronounced influence of sample removal and homogenisation on the results.^{6–7} The measurement of prostaglandin formation from the endogenous substrate or from added exogenous arachidonic acid in mucosal biopsy specimens is additionally influenced by the conditions of incubation and the concentration of the substrate.^{17–19} Also, gastric mucosa has a high catabolic capacity for prostaglandins,^{17–20} making interpretation of the results obtained in whole tissue difficult. To overcome these problems, prostaglandin synthesis was assessed in the microsomal fraction, in which the enzymes of prostaglandin formation are localised, but where prostaglandin degradation does not occur.²¹

In earlier investigations into the effect of alcohol on prostaglandin production in gastric mucosa, the main line of approach has been to study the action of acute alcohol administration.^{6–8–22} Depending on the concentration of the alcohol administered, results have differed. Numerous studies have reported an inhibition of prostaglandin production in gastric mucosa of laboratory animals after the acute administration of concentrated alcohol (50%–100%) as used to produce mucosal necrosis in the stomach.^{6–8–22} On the other hand, experiments on rats to investigate the effect of the moderate concentrations of alcohol commonly found in alcoholic beverages showed an increase in PGF₁ formation²³ and in PGE₂ and PGF_{2α}-like material²⁴ has been reported. In humans, acute ingestion of 12.5%

alcohol reduced the output of prostaglandin E₂ in gastric juice, whereas the output of PGF_{2α} and 6-keto PGF_{2α} remained unchanged.¹¹

The effect of chronic administration of moderate concentrations of alcohol has, to date, been investigated only in animals. Feeding rats a liquid diet containing ethanol for one to three months reduced the capacity of gastric mucosa to synthesise PGE₂ by 40%–60%. The findings of this study – namely that chronic alcohol misuse was associated with reduced mucosal activity in terms of PGE₂ and PGF_{2α} synthesis – accords with the results obtained in these animal experiments.

The relevance of alcohol misuse as a cause of gastric mucosal injury including haemorrhagic erosive gastritis in humans has become apparent from several endoscopy studies.^{1–25} However, the pathomechanism of alcohol-induced mucosal damage has not been clarified. Suspected factors are disturbances in the permeability of the mucosa^{25–26} and in the microcirculation.^{1–25–27} Moreover, inhibition of protective mechanisms of the gastric mucosa – for example, the breakdown of the mucosal 'bicarbonate barrier'^{25–28} – brought about by the acute action of alcohol, might contribute to mucosal damage. The reduction in the ability to synthesise PGE₂ and PGF_{2α} shown in this study might have an influence on several of the factors considered to be of relevance for the pathogenesis of the alcohol induced mucosal injury in the stomach. PGE₂ stimulates gastric mucosal blood flow²⁹ and bicarbonate output,³⁰ as well as the production of mucus.³¹ Also PGE₂ inhibits the release of inflammatory mediators from intestinal mucosal mast cells such as platelet activating factor and tumour necrosis factor α.³² Moreover, a trophic effect of PGE₂ on mucosal epithelium has also been reported.³³

In the control group PGE₂ synthesis remained unchanged in patients with mild gastritis, where there was a significant increase in the patients with severe gastritis. On the other hand, gastritis was associated with a decrease in the ability to synthesise PGF_{2α}. Other studies on the effect of mucosal inflammation on the prostaglandin synthesis have produced varying results. When the activity of prostaglandin synthesis was measured after incubation of homogenates of gastric biopsy specimens with ¹⁴C-labelled arachidonic acid, no significant differences were seen in the sum of cyclooxygenase products (prostaglandins A₂+B₂, D₂, E₂ and F₂) in the mucosa of patients with erosive or non-erosive type B gastritis and controls with normal mucosa.³⁴ Similarly, no difference was found for the combined PGE₂ and PGF_{2α} content of biopsy specimens from the antrum in patients with and without mucosal inflammation.¹²

Smoking has been shown to influence prostaglandin metabolism in the mucosa of the stomach.^{12–35} Active smoking reduces PGE₂ concentration in gastric juice,³³ and decreases mucosal 6-keto-PGF₁ synthesis.³⁵ In another study significant decreases in mucosal prostaglandin content were found in biopsy specimens from the body and antrum of patients who had smoked within the two days immediately

preceding endoscopy.¹² Because in the present study the percentage of smokers was higher among alcoholic patients, smoking might contribute to the lower rate of PGE₂ production in these patients. However, active smoking did not significantly influence the results in terms of prostaglandin synthesis in the group of alcoholic patients.

The presence of *H. pylori* in the biopsy specimens had no influence on prostaglandin synthesis. This accords with the results of other studies on prostaglandin synthesis in homogenates of antrum specimens of patients with and without *H. pylori*.³⁴⁻³⁶ Moreover, the presence of *H. pylori* did not influence the content of PGE₂ in the antrum and body of the stomach.¹² Reduced PGE₂ synthesis in the mucosa of the antrum and corpus in *H. pylori* positive patients reported by others³⁷ might be explained by the type of measurement used, and also by the fact that values were expressed in terms of wet weight.

In patients with alcoholic cirrhosis and portal hypertension the PGE₂ content in biopsy specimens from the gastric antral mucosa was shown to be significantly lower than in controls without liver disease.³⁸⁻³⁹ In these studies the patients abstained from alcohol for more than two weeks³⁸ or eight days³⁹ respectively. In addition, PGE₂ content in cirrhotic patients without portal hypertension were not significantly different from the controls without liver disease.³⁸ Therefore, it was concluded that the decrease in PGE₂ tissue concentrations is related to the presence of portal hypertension.³⁹ In this study alcoholic patients with cirrhosis were excluded to avoid a potential overlap of the effect of portal hypertension with the effect of chronic alcohol misuse.

In conclusion, chronic alcohol misuse reduces the rate of synthesis of PGE₂ and PGF_{2α} in the gastric mucosa in humans. The decreased capacity for prostaglandin production might be a factor in the increased vulnerability of mucosa in alcoholic patients. The reasons for the reduced capacity for prostaglandin synthesis in gastric mucosa in alcoholic patients remain to be clarified.

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