Alcoholic beverages produced by alcoholic fermentation but not by distillation are powerful stimulants of gastric acid secretion in humans

S Teyssen, T Lenzing, G González-Calero, A Korn, R L Riepl, M V Singer

Abstract
Background—The effect of commonly ingested alcoholic beverages on gastric acid output and release of gastrin in humans is unknown.

Aim and Methods—In 16 healthy humans the effect of some commonly ingested alcoholic beverages produced by fermentation plus distillation (for example, whisky, cognac, calvados, armagnac, and rum) or by alcoholic fermentation (beer, wine, champagne, martini, and sherry) on gastric acid output and release of gastrin was studied. Gastric acid output was determined by the method of intragastric titration. Plasma gastrin was measured using a specific radioimmunoassay.

Results—None of the alcoholic beverages produced by fermentation plus distillation had any significant effect on gastric acid output and release of gastrin compared with control (isotonic glucose and distilled water). Alcoholic beverages produced only by fermentation significantly (p<0.05) increased the gastric acid output by 57% to 95% of maximal acid output (MAO) and release of gastrin up to 5·1-fold compared with control. If beer, wine, and sherry were distilled, only their remaining parts increased gastric acid output by 53% to 76% of MAO and increased release of gastrin up to 4·3-fold compared with control.

Conclusions—(1) Alcoholic beverages produced by fermentation but not by distillation are powerful stimulants of gastric acid output and release of gastrin; (2) the alcoholic beverage constituents that stimulate gastric acid output and release of gastrin are most probably produced during the process of fermentation and removed during the following process of distillation.

Keywords: alcoholic beverages, gastric acid output, gastrin, humans.

Although detailed epidemiological data on the frequency of peptic ulcer disease associated with alcoholism are scanty, patients with peptic ulcer disease are often advised to avoid alcoholic beverages. In addition, the pathophysiological mechanisms of damage to the gastric mucosa by ingestion of pure ethanol and common alcoholic beverages are still poorly understood.

An increased gastric acid and gastrin response to alcoholic beverages could be a possible pathogenic factor in peptic ulcer disease. Intragastric instillation of 500 ml of 1·4% and 4·0% (vol/vol) pure ethanol has a small stimulatory effect on gastric acid output with a response equal to about 23% of the pentagastrin stimulated incremental gastric acid output (maximal acid output (MAO)). Higher concentrations of pure ethanol (up to 40% vol/vol) have either no effect or a mildly inhibitory effect. None of the ethanol concentrations tested increase plasma gastrin concentrations1–3; for review see 10,11.

In contrast, some of the commonly ingested alcoholic beverages are potent stimuli of gastric acid output and release of gastrin. Oral or intragastric instillation of beer causes a stimulation of about 95% of that produced by pentagastrin (MAO). Red and white wine increases gastric acid output up to 61% of MAO. Both, beer and wine, cause pronounced release of gastrin. Beverages with a high alcohol content, such as whisky (40% vol/vol) and cognac (40% vol/vol) do not stimulate gastric acid output or release of gastrin.

The search for the stimulatory substances in beer shows that the powerful stimulants of gastric acid output are produced during the process of alcoholic fermentation and that they are thermostable and anionic polar substances with a molecular weight lower than 700 Daltons.12–15 It was also found that the known non-alcoholic ingredients in beer and wine are not responsible for the stimulatory action of both alcoholic beverages on gastric acid output and release of gastrin.8

Until the present investigation, it was not known why beverages with a high ethanol content (for example, whisky and cognac) do not stimulate gastric acid output and release of gastrin, whereas alcoholic beverages with a comparatively low ethanol content (for example, beer and wine) have a stimulatory effect. A possible explanation for the different effects between alcoholic beverages with a high or low ethanol content on gastric function might be their different production processes: beer and wine are produced by fermentation of carbohydrates (for example, glucose); whisky and cognac are produced by fermentation and subsequent distillation.
In addition, the action of commonly ingested before meal drinks (aperitifs and spirits other than whisky and cognac) on the stomach had not been studied until now.

The aim of this study was to investigate in non-alcoholic human volunteers the action of some alcoholic beverages with a high ethanol content produced by fermentation plus subsequent distillation, such as aperitifs and spirits, on the gastric acid output and release of gastrin, and to compare their effects with that of alcoholic beverages produced by fermentation, such as beer, champagne, sherry, and other aperitifs, because the action of these alcoholic beverages on gastric acid output is comparatively unknown. Some of these data have been published in abstract form.16

**Methods**

**SUBJECTS**

Sixteen healthy young volunteers (nine men and seven women, aged 21 to 31 years; body weight, 52 to 87 kg) were studied. All were in good health, were not receiving medication, and were either teetotallers or drank less than 20 g of pure alcohol each day. Twenty per cent were smokers (not more than 10 cigarettes per day). None of the volunteers was *Helicobacter pylori* positive (tested by a 13[C] urea breath test).17 Fully informed written consent was obtained from each subject, and the research protocol was approved by the University Hospital’s Ethics Committee. The investigation was carried out according to the principles of the revised declaration of Helsinki 1989.

Each subject was investigated several times on separate days. The sequence of tests was randomised, and not more than two tests per week were performed in each subject with a minimum interval of 48 hours between the tests.

**STUDY DESIGN**

**Test meal stimulated secretion**

Gastric acid output in response to various alcoholic liquid test meals was determined in 30 and 60 minute (see later) periods, respectively, by automatic titration to pH 5-5 with 0-5 mol/l NaOH as previously described18 with slight modifications.19,20 After an overnight fast (12 hours, during which the subjects also avoided smoking), a two luminal nasogastric tube (AN 10; H G Anderson Products, New York, NY) was positioned in the most dependent part of the stomach. The position was controlled by the ‘water-recovery test’ described by Hassan and Hobsley.21 The subjects were sitting in a slightly recumbent position. Before instillation of the first meal, the stomach was rinsed with water (100–150 ml) and emptied by aspiration; the intragastric titration was then started.

On each experimental day, five liquid meals (volume 500 ml each, pH 5-5) were instilled into the stomach in 30 or 60 minute intervals (see Fig 1A). After each period, the remaining gastric content was emptied, and the volume was measured. Thereafter, the next meal was instilled. The first two meals of each study consisted of isotonic glucose (5-76% wt/vol): this has been shown to inhibit gastric emptying without changing the acid secretory response.19 Thus, sufficient volume remained in the stomach for constant intragastric titration. Thereafter, 500 ml of one of the liquid test meals with an ethanol content less than 10% vol/vol (Table) was instilled into the stomach, and acid secretion was measured for one 60 minute period.

When alcoholic beverages with an ethanol content higher than 10% (vol/vol) were tested, a modification of the protocol was needed because intragastric instillation of 500 ml of these alcoholic beverages would not have been tolerable (Fig 1B). At the beginning of the test period, 125, 187, 250 or 300 ml (see Table), respectively of these meals was given intragastrically; 10 minutes later, 375, 313, 250 or 200 ml, respectively, of isotonic glucose (5-76% wt/vol) was added to have enough volume for intragastric titration (500 ml). The respective glucose control solutions were given in a similar manner.

To investigate the effect of the liquid test meals after ending perfusion, the actual test period was followed up by two control periods.

<table>
<thead>
<tr>
<th>Test meal</th>
<th>Ethanol content (% vol/vol)</th>
<th>Given volume (ml)</th>
<th>pH</th>
<th>Production process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>4-9</td>
<td>500</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>White wine</td>
<td>10-0</td>
<td>500</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>Champagne</td>
<td>12-0</td>
<td>300</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>Martini</td>
<td>15-0</td>
<td>250</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>Harvey’s</td>
<td>16-5</td>
<td>250</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>Remaining part (=supermatant) of distilled sherry</td>
<td>0</td>
<td>500</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>Remaining part (=supermatant) of distilled wine</td>
<td>0</td>
<td>500</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>Remaining part (=supermatant) of distilled beer</td>
<td>0</td>
<td>500</td>
<td>5-5</td>
<td>alcoholic fermentation</td>
</tr>
<tr>
<td>Scotch whisky (Ballentines)*</td>
<td>43-0</td>
<td>125</td>
<td>5-5</td>
<td>distillation</td>
</tr>
<tr>
<td>Cognac (Remy Martin)*</td>
<td>40-0</td>
<td>125</td>
<td>5-5</td>
<td>distillation</td>
</tr>
<tr>
<td>Calvados Hors d’Age</td>
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<td>125</td>
<td>5-5</td>
<td>distillation</td>
</tr>
<tr>
<td>Armagnac C les Deux</td>
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<td>125</td>
<td>5-5</td>
<td>distillation</td>
</tr>
<tr>
<td>Bacardi Superior Gold Rum</td>
<td>37-5</td>
<td>125</td>
<td>5-5</td>
<td>distillation</td>
</tr>
<tr>
<td>Pernod Fils</td>
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<td>125</td>
<td>5-5</td>
<td>distillation</td>
</tr>
<tr>
<td>Cointreau</td>
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<td>125</td>
<td>5-5</td>
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<tr>
<td>Campan</td>
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<td>500</td>
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<td>distillation</td>
</tr>
<tr>
<td>Distilled beer</td>
<td>4-9</td>
<td>500</td>
<td>5-5</td>
<td>distillation</td>
</tr>
</tbody>
</table>

*Results are taken from reference 2.
in which isotonic glucose was administered for 30 minutes each (data not shown).

Blood samples (6 ml) for determination of gastrin were drawn at 30 minute intervals during the control periods and at 10 minute intervals during administration of the test solutions (Fig 1). The blood was collected in ice chilled EDTA tubes containing 400 KIU aprotinin (TrasyloI) per ml of blood. The samples were centrifugated immediately at 4°C, and the plasma gastrin was frozen at −20°C. Plasma gastrin was measured using a specific radioimmunoassay (Becton Dickinson and Company, Orangeburg, New York, USA).

Blood samples (4 ml) for ethanol concentrations were drawn once at the end of the second control period before the test solutions were given, during the test period in 10 minute intervals, and during the last two control periods in 15 minute intervals. Serum concentrations of ethanol were determined by the alcohol-dehydrogenase method (Blutalkohol, C F Boehringer & Söhne GmbH, Mannheim, Germany).

Pentagastrin stimulated secretion
To determine the maximal acid output (MAO) and to ensure that gastric acid output was within normal limits (that the subjects were neither hyposecretors nor hypersecretors), a pentagastrin test (6 μg/kg subcutaneously) was performed in each subject. Gastric acid output was measured by intragastric titration. During the 60 minute basal period, two meals of isotonic glucose solution (500 ml each) were administered intragastrically. After subcutaneous exogenous administration of pentagastrin, another two isotonic glucose solutions were administered at 30 minute intervals.

TEST MEALS
Before instillation of the liquid meals (see Table), the pH of each solution was adjusted to 5-5 by addition of HCL or NaOH in the appropriate amount. In the upper part of Table all tested alcoholic beverages produced by the process of alcoholic fermentation are listed. In the lower part of Table all tested alcoholic beverages produced by the process of alcoholic fermentation and subsequent distillation are listed. Beer, wine, and sherry were distilled by the method of ‘patent-still’ (synonym: ‘continuous or coffey-still-method’). For a detailed description of the process of fermentation and distillation see specific reports (for example refs 22-25).

CULCATIONS AND STATISTICS
All statistical analyses were performed on incremental responses, that is, on observed gastric acid response minus response to intragastric isotonic glucose. To calculate the one hour incremental gastric acid output, the value obtained during the second 30 minute control period of intragastric glucose administration was multiplied by two, and this value was subtracted from the observed one hour gastric acid response to a given stimulus. This one hour incremental gastric acid output in response to the various test substances was calculated for each experiment and each subject, and these individual values were used for statistical analysis.

MAO was calculated by adding the two 30 minute outputs produced by subcutaneous injection of pentagastrin. To compare the gastric acid response to pentagastrin with that of the different test meals, the incremental MAO – that is, observed MAO in response to pentagastrin minus acid output during intragastric instillation of isotonic glucose – was calculated.

The integrated gastrin response for each dose of stimulant was calculated by the formula described by Taylor et al.26 All statistical analyses were performed on the integrated responses of gastrin.

The differences between the various treatments were evaluated using analyses of variance (ANOVA). p Values of <0.05 were considered significant. Data are reported as means (SEM) unless stated otherwise.

Results
Each subject had a normal gastric acid secretory response to pentagastrin. The mean basal gastric acid output in response to 500 ml isotonic glucose solution (5-8% wt/vol) was 10.7 (1-7) mmol/h. The mean MAO was 28.1 (2-3) mmol/h, and the mean incremental MAO was 17.4 (1-6) mmol/h (mean (SEM), n=16).

Intra gastric instillation of 500 ml distilled water did not significantly stimulate gastric acid output above basal (Fig 2).

Alcoholic beverages produced by fermentation
Of the alcoholic beverages produced only by fermentation tested, beer and champagne were the most potent stimuli of gastric acid output causing 85% and 95%, respectively,
of incremental MAO. The distillate of beer did not significantly increase gastric acid output, whereas the remaining part of the distilled beer still caused an increase in gastric acid output of about 64% of incremental MAO (Fig 2).

The one hour incremental response to Martini Bianco was 57% of incremental MAO.

The one hour incremental gastric acid response to sherry was 83% of incremental MAO. The distillate of sherry did not cause any significant increase in gastric acid output, whereas the remaining part of the distilled sherry still caused an increase in gastric acid output of about 76% of incremental MAO (Fig 3).

The one hour incremental gastric acid response to wine was 61% of incremental MAO (results are taken from ref 2). The distillate of wine did not cause any significant increase in gastric acid output, whereas the remaining part of the distilled wine still caused an increase in gastric acid output of about 54% of incremental MAO (Fig 3).

**Alcoholic beverages produced by distillation**
Of the selected alcoholic beverages produced by distillation (calvados, armagnac, cointreau, and bacardi) none significantly changed gastric acid output compared with controls (Fig 2).

**Plasma gastrin concentrations**
Beer and champagne as well as martini, sherry, and the rest (remainder) of distilled beer, wine, and sherry significantly increased plasma gastrin concentrations up to 5.1-fold compared with control. Their one hour integrated gastrin responses are shown in Figures 4 and 5.

Plasma gastrin concentrations in response to alcoholic beverages produced by distillation and distilled beer, wine, and sherry were not significantly changed compared with control (isotonic glucose solution and water; Figs 4 and 5).

**Serum alcohol concentrations**
Serum alcohol concentrations in response to the different alcoholic beverages (Table) peaked within 20 to 50 minutes (in respect to their alcoholic concentrations up to 19.8 mmol/l) and did not reach basal values within two hours after ingestion of the various alcoholic beverages (data not shown).
Alcoholic beverages and gastric acid secretion

Discussion
The important new findings of this study are:
1. Alcoholic beverages that are produced only by fermentation, such as champagne, beer, white and red wine, sherry, and martini are strong stimulants of gastric acid output and release of gastrin in healthy, non-alcoholic humans.

2. Alcoholic beverages produced by fermentation and subsequent distillation, such as whisky and cognac, Pernod, Bacardi, and other spirits such as armagnac, calvados, cointreau do not stimulate gastric acid output and release of gastrin.

3. The distillation of beer, wine, and sherry results in the loss of their effect on gastric acid output and release of gastrin. This finding is proof that the distillation process is responsible for the loss of the stimulatory action of these beverages.

The finding that oral or intragastric instillation of beer is a potent stimulus of gastric acid output (>95% of MAO) and release of gastrin is confirmation of earlier studies by other investigators and ourselves. Until now, it was not known that champagne is a very powerful stimulus of gastric acid output (95% of MAO). This powerful action of champagne does not depend upon its content of CO₂.

In earlier studies, we have shown that red and white wine, which are produced by alcoholic fermentation, are also powerful stimulants of gastric acid output and release of gastrin. In this study, we observed that sherry, which is produced on the basis of wine, is almost as potent as beer and champagne (83% of MAO). When sherry is distilled, no significant stimulatory action of the distillate on gastric acid output and release of gastrin is observed, whereas the remaining part (=supernatant) is still a potent stimulus. Thus, the distillation process is responsible for the loss of the stimulatory action of this beverage.

Alcoholic beverages, produced by fermentation plus distillation, such as aperitifs and spirits, had no stimulatory action on gastric acid output and release of gastrin. The ethanol content of beverages produced by distillation is high (above 40% vol/vol). It has been shown that intragastric instillation of 40% ethanol does not stimulate gastric acid output and release of gastrin; thus, ethanol is excluded as a causal factor for the

Figure 3: One hour incremental gastric acid output (nmol) in response to beer, wine, and sherry, their distillates and their remaining parts (=supernatants). For comparison, the mean one hour maximal acid output (MAO) in response to pentagastrin is also shown. Results are means (SEM) of six subjects and of 16 subjects for MAO. *p<0.05 compared with both distilled water and isotonic glucose (5−76% wt/vol) control solution (n=16).
Figure 4: One hour integrated plasma gastrin response (pM) to different alcoholic beverages. Results are means (SEM) of six subjects. *p<0.05 compared with distilled water and isotonic glucose (5.76% wt/vol) control solution (n=16).

non-stimulatory action of alcoholic beverages produced by distillation on the stomach.

During the distillation process of alcoholic beverages, inhibiting substances are generated, or stimulatory substances are removed as far as gastric acid output and release of gastrin are concerned. We favour the hypothesis that during the distillation process non-alcoholic substances, which have been generated during alcoholic fermentation and which stimulate gastric acid output and release of gastrin, are removed. The fact that the distillate of sherry, beer, and wine no longer stimulates gastric acid output and release of gastrin but the rest of sherry, beer, and wine still does is strong evidence for this hypothesis. We do not know whether the same inhibitory substance or substances are produced in all beverages tested and as a consequence are responsible for the non-stimulatory action of these beverages on gastric acid output and release of gastrin.

During previous years, we have looked intensively for the stimulatory substances in beer.8,12-15 None of the known stimulants of gastric acid output present in beer either alone or in combination could be implicated.8 Among the various preproducts of beer tested, only those products produced after the addition of yeast – that is, after the onset of fermentation – had any capacity to stimulate acid secretion. Fermented glucose was the most potent stimulant.8 To identify this metabolic product of yeast, fermentation of glucose extracts obtained from fermented glucose by different extraction methods (for example, ethylacetat extraction and eluate of anion exchange resin) were tested for their ability to stimulate acid secretion or gastrin release.12-15

Preliminary results suggest that the powerful stimulants of gastric acid output are thermostable and anionic polar substances with a molecular weight lower than 700 Daltons. We speculate that these substances are removed during distillation.

In conclusion, this study shows for the first time that alcoholic beverages produced by fermentation but not those produced by alcoholic fermentation plus distillation are powerful stimulants of gastric acid output and release of gastrin in healthy, non-alcoholic humans. The stimulatory non-alcoholic constituents of those alcoholic beverages that stimulate gastric acid output and release of gastrin are most probably produced during the process of fermentation of carbohydrates and removed during the following process of distillation. Their pronounced secretory effect on the stomach is perhaps mediated greatly but not exclusively by gastrin release.

Both, the inhibitory and, predominately, the stimulatory mechanisms of alcoholic beverages...
on gastric acid output and release of gastrin remain to be further elucidated.

12. Teysen S, Singer MV, Eysselin VE. Fermentation of carbohydrates by yeast is the major step for the powerful stimulatory action of beer on gastric acid secretion in humans. [Abstract]. Alcohol Alcohol 1991; 26: 261.
20. Lam SK, Isenberg JJ, Grossman ML, Lane WH, Walsh JH. Gastric acid secretion is abnormally sensitive
Teyssen, Lenzing, González-Calero, Korn, Riepl, Singer


