

## PROGRESS REPORT

## Alcohol and gastric acid secretion in humans

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**Abstract**

The secretory response of gastric acid to pure ethanol and alcoholic beverages may be different because the action of the non-ethanolic contents of the beverage may overwhelm that of ethanol. Pure ethanol in low concentrations (<5% vol/vol) is a mild stimulant of acid secretion whereas at higher concentrations it has either no effect or a mildly inhibitory one. Pure ethanol given by any route does not cause release of gastrin in humans. Alcoholic beverages with low ethanol content (beer and wine) are strong stimulants of gastric acid secretion and gastrin release, the effect of beer being equal to the maximal acid output. Beverages with a higher ethanol content (whisky, gin, cognac) do not stimulate gastric acid secretion or release of gastrin. The powerful stimulants of gastric acid secretion present in beer, which are yet to be identified, are thermostable and anionic polar substances. The effect of chronic alcohol abuse on gastric acid secretion is not as predictable. Chronic alcoholic patients may have normal, enhanced, or diminished acid secretory capacity; hypochlorhydria being associated histologically with atrophic gastritis. There are no studies on the acute effect of alcohol intake on gastric acid secretion in chronic alcoholic patients. The acid stimulatory component of beer and wine needs to be characterised and its possible role in the causation of alcohol induced gastrointestinal diseases needs to be investigated.

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Despite widespread interest in gastrointestinal diseases induced by alcohol the effects of acute and chronic exposure of the stomach to alcohol remain to be fully elucidated. A review of publications shows diverse and even contradictory results. For example, Lenz *et al*<sup>1</sup> found 5% and 10% ethanol to significantly stimulate gastric acid secretion whereas Singer *et al*<sup>2</sup> did not find any stimulatory effect. An explanation for these contradictions can often be traced to the experimental conditions of the different studies. Here we review the studies on the effect of ethanol and alcoholic beverages on gastric acid secretion in humans and discuss the possible reasons for the apparently discrepant results. We also consider the areas that need further research. There is considerable species variation in the response of the stomach to alcohol and so animal studies will be cited only where data from humans are inadequate.

**Effects of acute exposure of non-alcoholic subjects to alcohol on gastric acid secretion**

The effect of pure ethanol on gastric acid secretion has been investigated by several workers. Early uncontrolled experiments<sup>3,4</sup> suggested that alcohol had a stimulatory effect on gastric acid secretion; thus an 'ethanol test meal' was introduced to clinically evaluate acid secretory state in humans. Recent controlled studies have served to clarify the different aspects of the interaction between alcohol and gastric acid secretion. Gastric acid secretion is influenced by a number of factors such as pH, volume, osmotic activity, and caloric value of the infusate. The ideal osmotic control for ethanol is distilled water<sup>5</sup> and not hypertonic glucose or saline as has been used in some studies.<sup>1</sup> This is because ethanol is a non-electrolyte of small molecular weight that diffuses rapidly in and through biological membranes. Consequently the effective osmotic pressure that it exerts on biological membranes is far less than its osmotic pressure measured by an osmometer. Distilled water has an identical effect and is pharmacologically inactive. It is, therefore, considered the ideal osmotic control for ethanol (for detailed discussion see<sup>5</sup>). Because alcohol is also a source of energy (1 g of ethanol provides 7.1 kcal), it is necessary to have an additional caloric control. An equicaloric glucose solution is used for this purpose. To compare the effect of different substances on gastric acid secretion proper control solutions comparable with the test solution should be used. Unfortunately, not all studies have used proper controls and this may account for some of the contradictory results reported.

**Effect of pure ethanol on gastric acid secretion**

Intravenous infusion of different doses of ethanol<sup>6-8</sup> has been consistently shown to stimulate gastric acid secretion. Hirschowitz *et al*<sup>6</sup> infused 10, 20, and 40 ml of alcohol intravenously for thirty minutes and found a pronounced and dose dependent increase in acid secretion. Demol *et al*<sup>7</sup> found a 2.2-fold increase in output of gastric acid on infusion of 300 mg/kg of ethanol for 30 minutes followed by continuous infusion of 3 mg/kg/min for two hours. The dose used is comparable with those used by Hirschowitz *et al*.<sup>6</sup> Interestingly, Kölbel *et al*.<sup>8</sup> who used a higher initial dose of 600 mg/kg ethanol, found only a 55% increase in acid secretion. If a dose dependent increase in gastric acid secretion occurs in response to intravenous infusion of ethanol it must be in the lower dose range. With higher doses there seems to be a

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TABLE I Effect of intragastric ethanol on gastric acid secretion in non-alcoholic humans

Author	Dose of ethanol	Intragastric titration	Controls used	Effect
Cooke <i>et al</i> <sup>9-11</sup>	350 ml 5, 6, 8, 12, and 16% w/vol	No	Water	No effect
Lenz <i>et al</i> <sup>1</sup>	240 ml 5 and 10%	Yes	Hyp glu-sal*†	Significant increase
	240 ml 20%	Yes	Hyp glu-sal*†	No effect
Petersen <i>et al</i> <sup>12</sup>	720 ml/h 5%	Yes	NSal*	No effect
	300 ml/h 12%	Yes	NSal*	No effect
	100 ml/h 30%	Yes	NSal*	No effect
Singer <i>et al</i> <sup>2</sup>	500 ml 1.4 and 4%	Yes	DW*†	Mild stimulation (25% of MAO)
	500 ml 5, 6, 7, 8, 10%	Yes	DW*†	No effect
	240 ml 20%	Yes	DW*†	No effect
	120 ml 40%	Yes	DW*†	No effect

\*pH control used – all solutions brought to identical pH; †Isocaloric glucose solution used as caloric control; Hyp glu-sal = hypertonic glucose saline (used as osmotic and caloric control for ethanol); NSal = normal saline; DW = distilled water; MAO = maximal acid output.

negative effect on gastric acid secretion, the mechanism for which is not clear.

Studies on the effect of enteral infusion of ethanol have produced strikingly different results (Table I). Early studies by Cooke<sup>9-11</sup> showed that ethanol in concentrations of 1% to 20% did not stimulate gastric acid secretion. Lenz *et al*<sup>1</sup> used intragastric titration to measure acid output and hypertonic solutions of glucose saline as controls and found that 5% and 10% ethanol significantly increased three hour acid secretion whereas 20% ethanol had a mild but insignificant stimulatory effect. Subsequent studies have not, however, been able to show the stimulatory effect of 5% and 10% ethanol. In a well controlled study with isovolumetric, isosmotic and isocaloric controls Singer *et al*<sup>2</sup> studied the effect of intragastric bolus infusion of 1.4%, 4%, 5%, 6%, 7%, 8%, 10%, 20%, and 40% ethanol. By intragastric titration 1.4% and 4% ethanol were found to have a stimulatory effect on gastric acid secretion with a response equal to 23% and 22% respectively of the pentagastrin stimulated incremental acid output (maximal acid output – basal acid output). The higher concentrations of ethanol studied had either no effect or a mildly inhibitory one. Petersen *et al*<sup>12</sup> under similar controlled conditions found that slow intragastric infusion (28 g/h) of pure ethanol at concentrations of 5%, 12%, and 36% had no effect on gastric acid secretion. Thus we conclude that intravenous ethanol, at least in the doses used, and intragastric infusion of low concentrations (up to 5%) of ethanol stimulate gastric acid secretion whereas intragastric infusion of higher concentrations has either no effect or a mildly inhibitory one.

#### Effect of alcoholic beverages

Interestingly, the findings of the oral ethanol

TABLE II Effect of intragastric administration of alcoholic beverages on gastric acid secretion in non-alcoholic humans

Beverage	Dose	Effect	Author
Beer	360 ml	Pronounced increase	McArthur <i>et al</i> <sup>13</sup>
Beer	500 ml	Pronounced increase (equal to MAO)	Singer <i>et al</i> <sup>2</sup>
Beer	250 ml	7-fold increase compared with controls	Köbel <i>et al</i> <sup>14</sup>
Wine	240 ml	Pronounced increase >82% of MAO	Lenz <i>et al</i> <sup>1</sup>
Wine	300 ml/h	3-4-fold increase compared with control	Petersen <i>et al</i> <sup>12</sup>
Wine	500 ml	61% of MAO	Singer <i>et al</i> <sup>2</sup>
Whisky	150 ml	No effect	Cooke <i>et al</i> <sup>11</sup>
Whisky (10%)	240 ml	Mild increase	Lenz <i>et al</i> <sup>1</sup>
Whisky	125 ml	No effect	Singer <i>et al</i> <sup>2</sup>
Cognac	125 ml	No effect	Singer <i>et al</i> <sup>2</sup>

MAO = Maximal acid output.

ingestion experiments are exaggerated when alcoholic beverages are studied (Table II). Oral and intragastric infusions of beer were found to be potent stimuli of gastric acid secretion,<sup>2,13,14</sup> with a response of over 95% of that produced by pentagastrin.<sup>2,13</sup> This response was fourfold stronger than that produced by 4% ethanol.<sup>2</sup> Intrajeunal administration of beer also stimulated acid secretion, although the response was less than that to intragastrically infused beer.<sup>14</sup> Wine too proved to be a good stimulant of acid secretion, although not as good as beer, whereas 10% ethanol had no effect.<sup>2,12</sup> Beverages with higher alcohol content such as whisky and cognac did not stimulate acid secretion.<sup>2,11</sup>

#### Effect of acute exposure to alcohol on gastrin release

This aspect has been systematically studied by a number of workers including our group and allows some firm conclusions to be drawn. There is no direct correlation between acid secretion and gastrin release in response to alcohol (Table III). The facts that seem to emerge from analysis of the recent controlled studies are: (a) pure ethanol given intravenously, orally, or by an intragastric route, in different concentrations does not stimulate gastrin release whether or not it stimulates acid secretion<sup>1,2,7,9-12,15-17,20</sup>; (b) among the alcoholic beverages beer<sup>2,13-17,21</sup> and wine<sup>1,2,15-17</sup> produce pronounced stimulation of gastrin release whereas whisky, gin, cognac, and vodka do not have any effect on gastrin concentrations.<sup>1,2,11,15-19</sup> Here it is interesting to note that intrajeunal beer stimulated acid release without causing gastrin release.<sup>14</sup> The fact that the beverages with low alcohol content stimulate gastrin release whereas alcohol itself does not do so suggests that this response is mediated by the non-ethanolic component of the beverage.

#### Mechanism of action of alcohol on gastric acid secretion

It is clear that ethanol has a dual action on the secretory function of the gastric parietal cell; at low concentrations it stimulates gastric secretion and at high concentrations it has no effect or an inhibitory one. Studies have been done on humans, intact animals, isolated gastric mucosa, and gastric cell cultures to study the effect of ethanol on gastric cell function. The cellular mechanism of action of ethanol, however, remains to be fully elucidated.

Pure ethanol does not stimulate gastrin release in humans. Ethanol has a systemic as well as topical action on the gastric parietal cell. The persistence of the acid secretory response even after complete gastric emptying of ethanol administered by an intragastric route and the stimulatory action of intravenous ethanol imply a systemic action. The response to intravenous ethanol seems to be at least partially mediated by cholinergic nerves. After premedication with atropine intravenous ethanol failed to stimulate acid secretion. Atropine given during intravenous infusion led to an immediate fall in acid output.<sup>6</sup> Köbel *et al*<sup>8</sup> also found that atropine significantly reduced but did not abolish the

TABLE III Effect of ethanol and alcoholic beverages on gastrin release in non-alcoholic humans

Test solution	Dose	Effect	References
Ethanol	80 to 500 ml of 1.4 to 40%	No effect	1, 2, 10-12, 15-17, 20
Beer	250 and 500 ml	Strong release	2, 13-17, 21
Wine	240, 300, and 500 ml	Strong release	1, 2, 12, 15-17
Whisky	125 and 150 ml	No effect	1, 2, 11, 15
Gin	125 ml	No effect	16, 17
Cognac	125 ml	No effect	2
Vodka	60 and 250 ml	No effect	18, 19

effect of intravenous ethanol. Similar studies need to be done to evaluate the role of the cholinergic nerves in the gastric response to intragastric ethanol. A topical stimulatory action of ethanol on gastric acid secretion is seen at low concentrations (1%–5%). Studies with intragastric titration have noted an immediate acid secretory response to ethanol instillation before systemic absorption can occur. This action is independent of extrinsic innervation. In a recent study Chacin *et al*<sup>23</sup> recorded the effect of different concentrations of ethanol and some alcoholic beverages on the isolated toad gastric mucosa. The responses were similar to those reported from human studies. They found that low concentrations (1%–5%) of ethanol significantly stimulated acid secretion and cell respiration. The effect on cell respiration persisted even after blockade of the proton pump suggesting that this effect was primary and not secondary to stimulation of acid secretion. Low concentrations (1%–5%) of ethanol caused an increase in the content of cyclic AMP in human corporic gastric mucosa *in vitro*.<sup>24</sup> They also caused a dose dependent increase in activity of histamine sensitive gastric adenylate cyclase in guinea pig gastric mucosa.<sup>25</sup> Thus ethanol, apart from having an overall stimulatory effect on gastric parietal cell metabolism, seems to specifically stimulate gastric acid secretion through an increase in cyclic AMP and subsequently adenylate cyclase.

The mediator for the action of ethanol on the parietal cell is not known. Histamine has long been considered<sup>26</sup> a putative mediator of the gastric acid secretory response to ethanol. The stimulatory effect of ethanol on isolated toad gastric mucosa<sup>23</sup> was partially inhibited (–50%) but not abolished by cimetidine, suggesting that

the stimulatory action of low concentrations of ethanol on the gastric parietal cell is partly mediated through activation of H<sub>2</sub> receptors. It is possible that ethanol liberates histamine from cells containing histamine in the gastric mucosa. Earlier studies<sup>27–29</sup> with less accurate methods for measurement of histamine, however, failed to detect increase in histamine in the gastric tissue<sup>27</sup> or venous or arterial blood<sup>28, 29</sup> after stimulation with ethanol. These studies need to be repeated with presently available more accurate methods for assay of histamine. In the human stomach histamine is stored predominantly in the mast cells.<sup>30</sup> It would be interesting to see if ethanol stimulates release of histamine from mast cells in culture. Because it is also present in some beverages histamine was thought to be responsible for the acid secretory capacity of the beverages. In our study, however, we found no stimulatory action when the amines present in beer were given at doses present in the beverage.<sup>21</sup> The concentration seems to be too low to influence gastric acid secretion. In the study by Chacin *et al*<sup>23</sup> quoted earlier the stimulatory action of ethanol persisted even in calcium free solutions implying that extracellular calcium is not essential for its action. Parietal cell cultures could also be used to study the interaction between ethanol and the receptors for acetylcholine, gastrin, and prostaglandins. Further studies are clearly needed to fully elucidate the effect of ethanol on the gastric parietal cell.

The exact reason why beverages with higher ethanol content do not stimulate acid secretion is also not known. This could be due to several factors:

(a) Their inability to stimulate gastrin release. This could itself be due to a direct damaging or inhibitory effect on antral G cells or a lack of substances present in beer and wine that stimulate gastrin release. To see whether it is the high alcohol concentration or the possible lack of stimulants or their inability to act in the presence of high alcohol concentrations that is responsible for the absence of stimulatory action of whisky it would be interesting to study the effect of a simultaneous intragastric infusion of beer and

TABLE IV Acute effects of intragastric administration of beer, its preproducts (\*), beer extracts, and components of fermented glucose on gastric acid secretion and gastrin release

Test substance	Effect on acid secretion	Effect on gastrin release	Author
Beer	>93% of MAO	119% of the response to protein rich meal	Singer <i>et al</i> <sup>21</sup>
New beer*	>76% of MAO	110% of beer	Singer <i>et al</i> <sup>21</sup>
Finished wort*	46% of MAO	56% of beer	
Hop extract*	No effect	No effect	
First wort*	48% of MAO	49% of beer	
Components of beer (ethanol, amines, phenols Mg, Ca, L-amino acids, vitamins, organic acids, purines, pyrimidines)	No significant effect	No significant effect	Singer <i>et al</i> <sup>21</sup>
Lyophilised beer	pH dependent	No data	Singer <i>et al</i> <sup>21</sup>
pH 2.5	67% of beer		
pH 7.0	53% of beer		
pH 11.0	20% of beer		
Dialysed beer (Mol wt of contents >1000)	No effect	No data	Singer <i>et al</i> <sup>21</sup>
Unfermented glucose	No effect	No effect	Singer <i>et al</i> <sup>21</sup> Teyssen <i>et al</i> <sup>22</sup>
Fermented glucose	Equal to that of beer	114% of beer	Singer <i>et al</i> <sup>21</sup> Teyssen <i>et al</i> <sup>22</sup>
Contents of fermented glucose			
Polar substances	112% of MAO	108% of FG	
Semipolar substances	No effect	No effect	
Anions	61% of MAO	87% of FG	
Cations	No effect	No effect	
Neutral phase of anion-cation resin combination	No effect	No effect	
Thermostable substances	83% of MAO	No data	

MAO=Maximal acid output; FG=fermented glucose.

whisky. A lack of response would suggest that the high concentration of alcohol is the principal factor. The effect of alcohol and the beverages on antral G cells also needs further study.

(b) Damage to or inhibition of the gastric parietal cell. Davenport<sup>29</sup> found that ethanol solutions with a concentration above 10% produced mucosal damage. Beverages with concentrations above that in wine (10%–12%) failed to release gastrin or to stimulate acid. Therefore, it is possible that back diffusion of H<sup>+</sup> ions secondary to disruption of the mucosal barrier plays a part in the failure of these beverages to stimulate acid secretion. In the study by Chacin *et al.*<sup>23</sup> exposure of isolated toad gastric mucosa to 20% ethanol and rum and whisky produced a drastic, partially reversible inhibition of histamine stimulated acid secretion. Mechanisms for this effect needs further elucidation.

(c) Release of gastric acid inhibitors such as somatostatin. Intravenous infusion of ethanol has not been shown to release measurable amounts of somatostatin<sup>31</sup> but this does not exclude the possibility that somatostatin may mediate the inhibitory effect on the parietal cells. Prostaglandins inhibit acid secretion and their synthesis and release by gastric mucosal cells is enhanced by exposure to ethanol.<sup>32</sup>

(d) High osmolarity. Substances with high osmolarity have been found to inhibit acid secretion. Because the effective osmotic pressure exerted by ethanol is far less than its measured osmotic pressure it is unlikely that high osmolarity plays a major part in the production of acid inhibition by ethanol.

Alcoholic beverages with low ethanol content stimulate gastric acid secretion by additional mechanisms. This is obvious from the fact that the response to beer and wine is many times higher than that to corresponding concentrations of ethanol. The strong release of gastrin stimulated by these beverages is clearly an important mediator of this response but it is possible that they may have a direct effect on the parietal cell as well. In the study by Chacin *et al.*<sup>23</sup> on isolated toad gastric mucosa beer and wine had an effect similar to low concentrations of ethanol. Beverages with high ethanol content like whisky and cognac have no effect probably because the inhibitory effect of the high concentrations of ethanol present in these beverages overwhelms the stimulatory effect of the non-ethanolic components.

What exactly the non-ethanolic components of beer and wine that stimulate gastrin release are is unclear. Table IV gives the results of recent studies to identify these components. None of the known stimulants of acid secretion present in beer given alone or in combination could be implicated.<sup>21</sup> This is because the very low concentrations of these substances present in beer failed to stimulate acid secretion. 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.<sup>21</sup> To identify this metabolic product of yeast, fermentation of glucose extracts obtained from fermented glucose by different extraction methods (for example, ethyl acetate extraction,

eluante of anion exchange resin) were tested for their ability to stimulate acid secretion and gastrin release.<sup>22</sup> These preliminary results suggest that the powerful stimulants of gastric acid secretion are thermostable and anionic polar substances. Further studies need to be done to precisely identify them. It is also not known if spirits such as whisky also contain these byproducts of fermentation or whether they are removed during the process of distillation. Because one or more non-ethanolic components of the beverages are responsible for the release of gastric acid and gastrin it is possible that they may be partly responsible for the detrimental effects of alcohol abuse. Would beer free of these components be less harmful? As the different alcoholic beverages have not been shown to cause different diseases it is possible that alcohol itself is the most harmful component of the beverages.

#### Effect of chronic alcoholism on gastric acid secretion

Does chronic alcohol abuse change the gastric response to alcohol? All the results found in studies on non-alcoholic subjects may not hold true for chronic alcoholic patients. The stomach's adaptive capacity may change its response to alcohol, but there are few studies that have considered this problem.

The gastric acid secretory capacity in chronic alcoholic patients and those with alcoholic pancreatitis has been studied, with contradictory results reported by different studies. Chey *et al.*<sup>33</sup> found hyposecretion of gastric acid or achlorhydria in chronic alcoholic patients without clinical or laboratory evidence of pancreatic disease. Gullo *et al.*<sup>34</sup> studied 20 patients with chronic pancreatitis, of which 18 had histories of heavy alcohol abuse. About half (55%) had acid secretion in the normal range, one third (35%) had acid hypersecretion, and 10% had achlorhydria. Piubello *et al.*<sup>35</sup> found acid hypersecretion in a group of 21 chronic alcoholic patients and the peak acid output values in these patients were similar to those measured in patients with duodenal ulcers and was significantly higher than those in control groups. The study by Dinoso *et al.*<sup>36</sup> possibly gives the reason for these widely varying results. They studied the acid output in 70 chronic alcoholic patients and age matched normal healthy controls and correlated the results with mucosal histology. Although the mean maximal acid output of the group of chronic alcoholic patients was no different from that of controls, there was wide variation in the acid output within this group. The 15 alcoholic patients with atrophic gastritis had very low acid outputs whereas in those with superficial gastritis the values were only slightly lower than in normal subjects. Eight subjects with normal mucosa had acid hypersecretion (acid output >35 meq/h) compared with only one of 40 controls. The percentage of patients with normal mucosa was significantly less in the alcoholic group compared with the normal groups. Atrophic gastritis and superficial gastritis were more often seen in the alcoholic patients, which accounted for the hypochlorhydria seen in a group of these patients. When followed up with

serial biopsies one third of 12 patients with atrophic or superficial gastritis showed considerable increases in their maximal acid output, which paralleled the histological improvement seen in these patients. Further studies are needed to confirm these findings.

Acid hypersecretion found in a subgroup of alcoholic patients in these studies<sup>34-36</sup> also occurred in dogs chronically given alcohol. This was attributed to increase in mean parietal cell mass,<sup>37</sup> a threefold increase in mean parietal cell volume accompanied by mitochondrial hypertrophy, and a pronounced increase in the secretory tubular apparatus of the parietal cells.<sup>38</sup> There are no studies on the effect of acute alcohol intake on gastric secretion in the chronic alcoholic patient.

#### Effect of chronic alcoholism on gastrin release

There is only one study (published as an abstract) that reports on the effect of alcohol on gastrin release in the chronic alcoholic patient. In this study Hajnal *et al*<sup>39</sup> found a noticeably impaired gastrin release in response to a meal, ethanol, and wine. Although the gastrin release in response to wine was diminished compared with controls it was still higher than the response to ethanol. Clearly a study needs to be done with chronic alcoholic patients. This should be conducted soon after admission to hospital to assess the effect of commonly consumed alcoholic beverages on gastrin release and gastric acid secretion and the results should be compared with gastric histology. It would also be important to know if the changes found reverse with abstinence.

Thus recent controlled studies permit us to draw reasonably firm conclusions about the effect of ethanol and alcoholic beverages on non-alcoholic human subjects. Similar studies need to be done in chronic alcohol abusers. Further characterisation of the non-ethanolic component of beer and wine that stimulates acid and gastrin secretion needs to be carried out. This may throw more light on the mechanism of action of the alcoholic beverages on the gastric mucosa and possibly on other organs.

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