Review

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Do We Need Gastric Acid?

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Abstract
Evidence from comparative anatomy and physiology studies indicates that gastric acid secretion developed during the evolution of vertebrates approximately 350 million years ago. The cellular mechanisms that produce gastric acid have been conserved over the millennia and therefore proton pump inhibitors have pharmacological effects in almost all relevant species. These observations suggest that gastric acid provides an important selective advantage; however, in modern-day humans the need for gastric acid can be questioned in light of the widespread use of safe and effective pharmacologic acid suppression. The Kandahar Working Group addressed questions concerning the need, production and effects of gastric acid, specifically: (1) motility in the upper gastrointestinal (GI) tract; (2) neuroendocrine factors; (3) digestive and mucosal processes; (4) microbiology, and (5) central processes and psychological involvement. We addressed each topic with the individual models available to answer our questions including animal versus human studies, pharmacologic, surgical as well as pathophysiologic states of acid suppression.

Introduction

Evidence from comparative anatomy and physiology studies indicates that gastric acid secretion developed during the evolution of vertebrates approximately 350 million years ago. The cellular mechanisms that produce gastric acid have been conserved over the millennia and therefore proton pump inhibitors (PPIs) have pharmacological effects in almost all relevant species. These observations suggest that gastric acid provides an important selective advantage; however, in modern-day humans the need for gastric acid can be been questioned in light of the widespread use of safe and effective pharmacologic

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Gastric Acid and Motility

The effect of gastric acid on gastric motility and emptying has been neglected in the recent literature. Moreover many 'established facts' are based on small, short-term observational studies in healthy volunteers or in animal models. Four central issues concerning the interaction of gastric acid and function are addressed in this review, namely the effects of (1) acid instillation in the stomach and small bowel, (2) patho-physiologic states of acid secretion, (3) pharmacologic and (4) surgical acid suppression.

Acid Instillation in the Stomach and Small Bowel

Early animal studies have shown a dose-dependent delay of gastric emptying after instillation of organic acids (i.e., an inverse relationship between gastric emptying rate and hydrogen ion concentration). Increasing the molecular weight of the organic acids also inhibited gastric emptying; however, increasing the instilled volume accelerated the process [1]. More recently, Holzer et al. [2] confirmed that instillation of physiologic concentrations of hydrochloric acid delayed gastric emptying in a rat model, an effect that was blocked by atropine, suggesting involvement of a vagal mechanism.

The effects of small bowel acid exposure on gastric emptying are also inhibitory. Lin et al. [3] used a dog model in which they exposed different lengths of small bowel with different concentrations of acid. A dose-dependent inhibition of gastric emptying was demonstrated. This effect increased as longer segments of small bowel were exposed to acid; however, no effect was observed beyond the proximal 150 cm of jejunum. Other authors reproduced these findings and demonstrated that vagotomy attenuates the effects of gastric acid instillation on motility [4].

Although acid receptors in the stomach may inhibit gastric emptying directly, these studies suggest that the inhibitory effect of acid on gastric emptying is mediated by pH receptors in the proximal small bowel [4, 5]. This effect probably serves to maintain neutral pH for efficient small bowel digestion. Given the large volume of gastric acid secretions (1.5–2.5 liters/day), efficient feedback mechanisms are mandatory to ensure effective buffering of acid leaving the stomach and the appropriate interaction between gastric and small bowel function.

Pathophysiologic States of Acid Secretion

It has been shown that gastric emptying is delayed in patients with atrophic gastritis compared to healthy controls [6]. In this condition plasma levels of gastrin are inversely related to gastric emptying and, consistent with this finding, patients with residual acid secretion have faster emptying rates than those with achlorhydria [6]. However, the effect of gastrin on gastric function is not straightforward because in patients with chronic hypergastrinemia, such as the Zollinger-Ellison syndrome, no consistent changes in gastric emptying are seen [7]. This paradox may be explained by the effect of gastrin on secretion volume. Classic studies by Hunt and Stubbs [8] have shown that large volumes empty from the stomach faster than small volumes. In atrophic gastritis elevated levels of gastrin represent a feedback response to decreased gastric secretion from diseased mucosa, whereas in Zollinger-Ellison syndrome pathological levels of gastrin from a neuroendocrine tumor drive excessive gastric secretion. Thus, in these pathophysiologic states, the effect of gastrin on gastric emptying may be counteracted by changes in gastric secretion volume. This explanation is supported by a study that showed that replacement of gastric secretions (including acid and pepsin) normalized emptying and improved trituration of solid foods in patients with atrophic gastritis [9].

Pharmacologic Acid Suppression

In the fasted state, acid suppression increases phase 3 migrating motor complex (MMC) activity ('housekeeping contractions' that clear the bowel of undigested debris), whereas stimulating gastric acid secretion decreases MMC activity [10, 11]. This is likely due to alkaline pH in the duodenum triggering this contraction pattern [10].

In the fed state, most (but not all) studies show that acid suppression with H_2-receptor antagonists (H_2RA) and PPIs delays gastric emptying of solid food, although effects on liquid food are less consistent [9, 12–15]. Interestingly the delay in solid emptying is associated with vigorous antropyloroduodenal (APD) contractions (with-

out a change in peristaltic frequency) [16]. It has been suggested that the combination of increased APD activity and delayed gastric emptying indicates poor coordination of antral contraction with pyloric opening. However, it is also possible that acid suppression impairs chemical digestion and more vigorous mechanical breakdown of solid foods is required before gastric contents can pass through the pylorus [9, 17]. As in atrophic gastritis, pharmacologic acid suppression leads to hypergastrinemia [18, 19]. Studies have shown that intravenous infusion of gastrin increases antral activity and delays gastric emptying [16]. Moreover reduced gastric secretion volume on H_2RAs or PPIs would also be expected to slow gastric emptying [11]. However, the relative importance of acid suppression on secretion volume and motility with regard to gastric emptying is unknown.

Surgical Acid Suppression

In contrast to pharmacologic acid suppression, the effects of highly selective vagotomy on the gastric body (i.e., denervating the parietal cells but sparing the pylorus) in patients with peptic ulcer disease has been subject to long-term follow-up with regards to gastric motility and acid suppression [20–22]. Delayed gastric emptying is common in the early post-operative period; however, gastric function normalizes in the majority of patients at repeat testing after 6–12 months [20, 21], an effect that is maintained for at least 10 years despite a sustained reduction in basal and stimulated acid output [22].

Summary

Gastric acid has effects on upper GI functions in animal models and healthy volunteers. Acid-sensitive receptors provide feedback regulation that prevents the passage of excess gastric acid into the small bowel and maintains a pH environment conducive to efficient digestion. In disease states as well as pharmacologic studies, reduced acid secretion appears to delay gastric emptying; however, it is difficult to differentiate the effects of secretion volume and acid production on this process, and the clinical importance of this observation remains uncertain. Firstly, it has not been established that this effect is associated with symptoms of gastric retention or clinically relevant maldigestion. Secondly, no long-term follow-up data has been published. Although surgical procedures such as highly selective vagotomy may have direct effects on gastric function that delay emptying, it is interesting to note that these return to normal within a year. Thus, at least in the post-operative state, there appear to be compensatory mechanisms that can normalize gastric emptying despite a sustained reduction in gastric acid secretion. Similarly, the effects on gastric emptying and motility are reproducible in different states of acid suppression but have not been shown to be clinically relevant and seem to be compensated in the mid- to long-term. Further studies are required to address whether patients experience symptoms directly or indirectly related to delayed gastric emptying during pharmacologic acid suppression, and to assess whether gastric function returns to normal over time.

Neuroendocrine Regulation of Gastric Acid Secretion

Cranial, Gastric and Postgastric Secretory Responses

Gastric acid secretion is subject to a complex regulation by endocrine, paracrine and neurocrine mediators that interact extensively. Even before ingestion, the sight and smell of food leads to acetylcholine release from vagal nerve fibers that stimulates acid production via stimulation of M_3 receptors on parietal cells and also, indirectly, by increasing histamine release via acetylcholine receptors on the surface of ECL cells. Intragastric distension and an increase in luminal pH, together with certain nutritional factors (e.g., calcium), further promote gastric acid secretion via release of gastrin from antral G cells. Gastrin mediates its stimulatory action on parietal cells mainly via the blood stream and induction of histamine release from ECL cells in the proximal stomach, but also has a direct stimulatory effect on parietal cells via cholecystokinin (CCK-B) receptors. This alternative pathway is probably of minor physiological importance. The most important physiological inhibitor of gastric acid secretion is somatostatin secreted by antral D cells in response to low intraluminal pH. This inhibits gastrin release and gastric acid secretion directly via receptors on parietal cells and indirectly by inhibiting histamine secretion from ECL cells. In humans CCK is a potent stimulant for somatostatin release acting via CCK-A receptor, thereby inhibiting gastrin secretion [23]. Another potent inhibitor of gastric acid secretion is secretin. Its release is stimulated by duodenal acid and the effect is also mediated mainly by somatostatin [24, 25]. Numerous other neurohormonal peptides involved in the GI response to feeding, including GIP, GLP-1, GLP-2, PYY, VIP, galanin and GRP also regulate gastric acid secretion via actions on gastric G, ECL and D cells, respectively [26–33].The effects are largely inhibitory and exerted via central feedback.

The Effect of Ghrelin on Gastric Secretion

This review focuses on the effects of recently discovered enterohormones on gastric acid secretion, in particular ghrelin, an orexigenic peptide produced to 80% by the gastric oxyntic mucosa (X/A cells), but to a minor degree also in the central nervous system [34, 35]. Ghrelin accelerates gastric emptying in experimental animals and humans by inducing 'fasting' type 3 MMC activity [36]. The role of ghrelin in the regulation of gastric acid secretion is accepted; however, interpretation of findings is difficult as its effects are dose dependent and vary with the mode of delivery [37–44]. Following intravenous application [5–20 μg/kg (≙1.5–6 nmol/kg), molecular weight of ghrelin: 3,314 g/mol] in rats, stimulation of gastric acid secretion was observed which was almost equipotent to histamine (3 mg/kg i.v.). The anticholinergic atropine and cervical vagotomy, but not an H_2-receptor antagonist inhibited this effect [40]. Similarly, whereas relatively low doses of intraperitoneal ghrelin [5–80 μg/kg (≙1.5–24 nmol/kg)] increase gastric acid output [43], high doses of ghrelin (1–30 nmol/kg i.v.) given to rats with chronic gastric fistula or subcutaneously (1–10 nmol/kg) had either no effect on gastric acid output or inhibited acid output [41]. The central effects of intracerebroventricular ghrelin on gastric acid secretion are dose dependent and inhibitory at low doses (0.1 pmol/rat to 1 nmol/rat, maximum effect: 1 pmol/rat) in conscious rats, suggesting a tonic inhibitory role of ghrelin in the central control of gastric secretion [38]. Conflicting results reported in urethane-anesthetized rats during intracerebroventricular application of ghrelin (0.3, 0.6 or 1 nmol/rat) [42] may be due to the effects of urethane on somatostatin release or, once again, to higher dosages used in the latter study. Taken together, peripheral application of low doses of ghrelin stimulated gastric secretion in most studies while higher doses had no or even inhibitory effects. In contrast, central application of ghrelin in conscious rats inhibited acid output at very low doses, higher doses had less impact or resulted in stimulation. An intact vagal system was essential for mediating central and peripheral effects [40, 42, 44]. The apparently discrepant impact of peripheral and central ghrelin at various doses may be explained by the existence of different receptor subtypes: two isoforms have been identified, the predominantly central GHS-R_{1a} receptor and the GHS-R_{1b} receptor prevalent in the human fundus and antrum. The latter was thought to be inactive [45, 46] but has been attributed biological activity by recent authors [47, 48]. Cell culture experiments suggest that a further, unidentified subtype, or even subtypes, of ghrelin receptor also exists [46].

The following hypothesis could explain the observations described above. Central ghrelin exerts a (tonic) inhibitory control of gastric acid secretion via GHS-R_{1a} receptors at very low levels. Low levels of peripheral ghrelin release stimulate gastric acid secretion via GHS-R_{1b} receptors or an as yet unidentified novel receptor subtype. As ghrelin is produced in the stomach, additional activation of central GHS-R_{1a} receptors reverses the stimulatory effect. It has been observed that peripheral administration of ghrelin compared with intracerebroventricular application allows only limited access of the compound to hypothalamic sites. This may explain why high peripheral ghrelin concentrations are needed to induce inhibition [39]. Thus, under physiological conditions, the postprandial decrease in ghrelin plasma levels may release the inhibitory effect of central ghrelin and promote gastric acid secretion. It has to be emphasized that this scheme is based on the findings of animal studies as there have been no human studies on the effects of ghrelin on gastric acid secretion.

Other Recently Discovered GI Peptide Hormones

Amylin, a 37-aa peptide that shows 50% homology with the calcitonin-gene-related peptide, is colocalized with somatostatin in endocrine cells of the gastric fundus [52] and released in response to meal ingestion. Endogenous amylin stimulates somatostatin secretion via an autocrine pathway, resulting in an inhibition of histamine and acid secretion [53]. Adrenomedullin, another member of the calcitonin family, is localized in ECL and chief cells in the oxyntic mucosa. Similar to amylin, it stimulates somatostatin secretion and thus inhibits histamine and acid secretion [54, 55]. Different to amylin, the effect appears to be mediated via activation of intramural gastric fundic neurons since it is abolished by the axonal blocker tetrodotoxin [55]. The neuropeptide pituitary adenylate cyclase-activating peptide, which belongs to the glucagon/VIP family, stimulates both release of histamine from ECL cells and somatostatin release [56–58]. The resulting effect on gastric acid secretion is discussed inconsistently in the literature and depends on the species and experimental model used.

Summary

The control of gastric acid secretion depends on the central and peripheral effects of neuroendocrine hormones mediated directly and via vagal activity on the stomach. The initial cephalic and gastric response is predominantly stimulatory to gastric digestion, whereas the postgastric effects are inhibitory to maintain the correct

intestinal pH for intestinal digestion. Numerous neurohormones have been attributed to play a part in the regulation of gastric acid secretion. Whereas gastrin, CCK and GLP-1 together with the more recently discovered GLP-2 are known to regulate gastric acid production, ghrelin and amylin yield dose- and application-dependent changes too inconsistent to clearly establish their role and human studies are largely unavailable.

Gastric Acid and Digestive and Mucosal Processes

Calcium Absorption

The dissociation of food calcium complexes and the liberation of Ca^{2+} from calcium salts is strongly dependent on pH. This has led to the assumption that the presence of gastric acid is a necessary prerequisite for intestinal Ca^{2+} absorption. The negative effect of gastrectomy [59–61] or pernicious anemia [62] on bone mass supports this hypothesis. Moreover, a recent epidemiological study in patients older than 50 years revealed an increased risk of hip fracture in patients on long-term PPI [63]. Calcium is absorbed by two mechanisms: solubilization and conversion into its ionized form (Ca^{2+}) is efficient at low gastric pH and active absorption occurs in the duodenum and jejunum [64–67]. Passive calcium uptake occurs predominantly in the distal intestine and can compensate deficits in the active absorption pathway with high oral calcium uptake. Animal studies have yielded conflicting results regarding the influence of gastric acid on Ca^{2+} absorption, and some suggested normal overall Ca^{2+} intake at high oral intake even after complete suppression of gastric acid secretion [68, 69]. However, recent trials in humans, including both normal subjects and high-risk populations (postmenopausal women, patients on dialysis) showed that the oral application of calcium results in a serum peak of ionized as well as protein-bound calcium, which is missing in the presence of a complete blockade of gastric acid [70–72]. Furthermore it has been shown that the total intestinal calcium resorption was significantly reduced in postmenopausal women during high-dose PPI intake [73]. Gastrectomized rats rapidly lose bone mass [74–77], and in humans, gastrectomy also leads to osteopenia. The pathophysiology is multifactorial and may include hypergastrinemia, malabsorption, lack of oxyntic mucosa, vagal dysregulation with a disturbance of the gastrin-parathyreoid axis, and bacterial overgrowth. But also non-resective operations, like supraselective vagotomy, or disease, like pernicious anemia, result in osteopenia and an increased bone turnover.

In addition to reducing calcium absorption by inhibiting gastric acid, experimental studies have demonstrated that the inhibition of proton pump activity in osteoclasts has direct inhibitory effects on bone resorption and release of bone calcium [78, 79]. Although this effect may be discussed as a protective direct effect on bone tissue, it could further impair calcium metabolism and is another mechanism by which PPIs might contribute to the increased risk of hip fractures in elderly patients [63]. These patients require careful review as to their need for oral Ca^{+} supplements and other forms of osteoporosis prophylaxis.

Hematinic Absorption

Dietary iron, present in food as either heme iron or non-heme iron, is absorbed predominantly in the duodenum. Acid is important for solubilization, reduction and subsequent absorption of dietary iron. Decreased absorption has been reported in patients with hypochlorhydric conditions, such as gastrectomy, vagotomy, multifocal atrophic gastritis and autoimmune gastritis. Therefore, clinical monitoring of anemia and iron levels in gastrectomized patients or during long-term acid secretion seem reasonable [80–87].

Hypochlorhydria affects also the absorption of vitamin B_{12} (cobalamin) [88–92]. The vitamin is protein bound and is released in the presence of acid and pepsin. Vitamin B_{12} is subsequently bound to haptocorrins and passes into the small intestine. There cobalamin is liberated by pancreatic proteases and bound to intrinsic factor, which protects the vitamin from catabolism by intestinal bacteria. Intrinsic factor also mediates the absorption in the terminal ileum. Reduced cobalamin assimilation has been observed in patients with chronic gastric hyposecretion, such as during chronic atrophic gastritis [93–96], long-term therapy with PPIs [90] and after vagotomy [92, 97]. Especially subsets of *Helicobacter-pylori*-infected persons have an increased risk to develop cobalamin deficiency. It remains unclear whether this is a direct effect of hypochlorhydria or indirect via small intestinal bacterial overgrowth. Nevertheless, periodic assessment of cobalamin levels has been recommended for patients on chronic anti-secretory therapy [90]. Patients with pernicious anemia have a normal life span on B_{12} substitution therapy [98].

Protein and Lipid Metabolism

Acid secretion from gastric parietal cells facilitates protein and lipid digestion [99]. Pepsinogen, the most potent protease, is produced in gastric chief cells and is ac-

tivated under acidic conditions below a pH level of 4. Under hypochlorhydric conditions, impaired digestion of proteins occur and malabsorption of proteins has been observed [100, 101], although muscular atrophy or weight loss are rare. In addition, small intestinal bacterial overgrowth in hypochlorhydria probably leads to reduced breakdown of the metobolically useful products of protein and lipid digestion, thereby reducing their availability for certain essential amino and fatty acids (e.g., tryptophan, tyrosine and arachidonic acid). This effect has been suggested as a precipitating factor for depression (tryptophan is a precursor of serotonin) and other health problems in hypochlorhydric patients [89].

Differentiation and Regeneration of the Mucosal Epithelium

The differentiation of the gastric epithelium depends on the presence of gastric acid. The human epithelium in the GI tract belongs to the most quickly regenerating tissues in the body. All types of stomach epithelial cells are derived from a single progenitor cell in each gland. These stem cells are able to divide and to proliferate continuously. In mice (HK-ATPase knock-outs) or rats artificially depleted of gastric acid (gastrectomy), the normal differentiation process is disturbed so that metaplastic cells arise and gastric function is altered [74–76]. The presence of acid affects the healing of ulcers and regeneration. Artificial ulcers generated in rats lead to the release of growth factors at the topical site of the mucosa. Several of the growth factors, such as the hepatocyte growth factor, are activated only in acidic milieu, and ulcer healing is paradoxically prolonged in the absence of acid in animal models [102].

The data concerning tissue differentiation and regeneration are contradictory. Gastric-acid-activated gene expression of CDx2 in cellular models such as keratinocytes leads to metaplasia, similar to the development of specialized intestinal metaplasia in the distal esophagus, i.e., Barrett's esophagus [103–107]. However, absence of acid in mouse models may also lead to the differentiation of parietal cells into a pre-parietal and metaplastic state, not able to express HK-ATPase. Long-term acid suppression increases gastric metaplasia type II and atrophy, especially in the presence of *H. pylori;* however, these cells appear to represent a de-differentiated state and long-term follow-up studies have not demonstrated an increased risk of gastric cancer [106, 108]. Nevertheless it is recommended that *H. pylori* is eradicated from patients requiring long-term acid suppression.

Summary

Gastric acid affects the solubilization, digestion and absorption of several key nutrients. The importance of acid secretion is not critical under physiological conditions in patients taking a normal western diet; however, pathologic conditions including chronic gastric inflammation, gastric atrophy and hypochlorhydria help reveal the contributory role of gastric acid. The need for calcium, iron and vitamin supplements should be monitored during long-term PPI treatment in high-risk patients, such as postmenopausal women. Long-term acid suppression can also lead to mucosal gastric metaplasia and atrophy. Although the risk of gastric carcinoma is not elevated, it seems reasonable to manage other risk factors (e.g., *H. pylori*) that may exacerbate these effects.

Gastric Acid, GI Flora and Infection

GI Flora

Ingestion of food and fluids via the oral route introduces bacteria and other microorganisms into the esophagus and upper GI tract. Disinfection of this material has been suggested as a major role for gastric acid, as both the stomach and the proximal small intestine are virtually free of bacterial pathogens [109]. If this role of gastric acid is so important, reduction or elimination of gastric acid should alter the flora of the stomach and small intestine.

Stomach

The acid environment of the stomach is a filter for bacteria from the oropharynx and from the swallowed food and drinks. Thus it is difficult to distinguish whether bacteria found in the stomach really colonize the stomach or whether these are transients. A recent genomic characterization of the gastric flora yielded 128 different strains of bacteria, 13 of which have not been characterized in vivo [110]. There is a relationship between gastric luminal pH and the number of organisms in diseases with reduced acid secretion [111–113] and during acid-suppression therapy [114–117]. This change seems to be dependent on the amount of gastric acid suppression as the increase in bacteria is greater with PPI than with H_2-RA [118–120]. Patients on acid suppression due to gastroesophageal reflux disease (GERD) treated with either PPIs or H_2-RAs have a similar prevalence of *H. pylori* but a higher prevalence of non-*H. pylori* bacteria than controls in gastric juice aspirations (61 and 60% vs. 29%, respectively). They are mostly oropharangeal species and very rarely anaerobic [120]. In a systematic review [121], there was an increase of bacteria

in gastric juice in 12 out of 13 studies, irrespective of the investigated drug, either H_2-RAs (cimetidine, ranitidine) [122–132] or PPIs (omeprazole) [118, 133–139]. Growth at the mucosal surface may be detected in about 50% of patients after long-term treatment with any type of effective antisecretory drug [119, 140]. There have been concerns that these bacteria may produce carcinogenic nitrosamines and increase the risk of gastric cancer, although there is no evidence that acid suppression increases nitrosamine production [119, 140]. This could be explained by the fact that bacterially produced nitrosamines are at least partly dependent on acid catalyzation, a chemical process which occurs optimally at a pH of 2. In contrast, acid suppression may decrease nitrosamine production, which could be most relevant at the gastro-esophageal border and cardia [141, 142].

The disease state of atrophic gastritis is associated with complete achlorhydria; however, also other secretory products (e.g., pepsinogen) are eliminated. In patients with atrophic gastritis there is a significant increase in total bacterial count of the gastric lumen, with predominantly coliform bacteria [143], but no data on the clinical consequence of these changes are currently available. Similarly an increase of coliform bacteria is observed after partial gastric resection and gastroenterostomy [143]. However, the postoperative changes of barrier function and motility changes are fundamental, so they cannot be attributed to changes in gastric acid secretion alone.

In summary, both the contamination of the gastric juice and the colonization of the gastric mucosa with non-*H. pylori* flora increased during long-term acid inhibition and they seem dependent on length and extent of acid elimination, the clinical significance of which remains to be determined [144].

Modulation of Acid Secretion by *H. pylori* and Risk of Intestinal Infection

H. pylori has been shown to modulate gastric acid secretion. However, the pattern in which modulation of acid secretion occurs varies from patient to patient. In *Helicobacter*-associated gastritis and *H. pylori*-associated duodenal ulcers increased acid secretion is found. It has been speculated that this is due to increased release of gastrin and diminished mucosal expression of somatostatin [145]. Bacterial products recognized via pattern recognition receptors and pro-inflammatory cytokines such as TNFα are likely to cause these changes. In gastritis involving the gastric corpus acid secretion is decreased [146]. The *H. pylori*-induced decrease of acid secretion has been reported to be moderate: a 24-hour intragastric pH monitoring showed an increase in pH in patients without *H. pylori* infection from 1.4 ± 0.1 to 1.6 ± 0.3 in patients with *H. pylori* infection (median ± SD; $p < 0.01$) [147]. *H. pylori*-associated mucosal atrophy may also contribute to reduced acid secretion; however this has not been correlated in detail.

Investigations whether *H. pylori*-associated decrease of gastric acid secretion increases the risk of typhoid fever did not show a causative role but a common risk of environmental exposure to both bacteria, e.g., poor hygiene [148]. In a similar study on the risk of cholera infection, the authors reported that the overall risk of cholera was not significantly increased among *H. pylori*-infected subjects; the risk of cholera of life-threatening severity, however, was significantly elevated [149]. It again is unclear whether suppression of acid secretion contributes to the risk of more severe cholera as the overall risk is not increased, which should be the case if an *H. pylori*-induced rise in gastric pH would predispose to more intestinal infections in general.

Small Intestine

There is evidence that continuous acid-suppression therapy can lead to bacterial overgrowth in the small intestine [150]. In a controlled prospective study, duodenal juice was obtained from patients on continuous 6-week PPI therapy and compared to controls. No patient in the control group had duodenal bacterial overgrowth, while in the omeprazole group bacterial overgrowth was found in 14 (56%) patients, and the number of bacteria in the duodenal juice of patients treated with omeprazole was distinctly higher compared with the control group. Besides bacteria from the oral cavity, fecal-type bacteria were present in 7 of 14 and anaerobic bacteria in 3 of 14 patients; however, there was no apparent sign of clinical side effects or significant consequences of duodenal bacterial overgrowth [150]. In a subsequent prospective randomized study these effects were more marked in patients on omeprazole compared with patients on cimetidine. Moreover, gastric pH was higher in patients with bacterial overgrowth compared with those without; findings that support the contention that the incidence of gastric and duodenal overgrowth is dependent on the level of acid suppression.

GI Infections

Stomach

It is well known that some enteric pathogens are more acid-resistant than others. *Escherichia coli* and *Shigella*

flexneri can both survive exposure to a pH of 2.0 ± 2.5, whereas *Salmonella enterica typhimurium* is killed following exposure to pH 3. The ability to survive at a low pH is thought to be one factor that determines the infective dose required to cause disease [121]. From these observations it has been concluded that the presence of gastric acid has important implications for the survival of pathogens that have entered the GI tract. Suppression of gastric acid secretion may allow infection to occur following ingestion of a smaller number of inoculated pathogens such as *Salmonella enterica* or *Listeria monocytogenes* [131, 137, 151]. There is some evidence to support an increased risk of parasitic infections under conditions of reduced acid secretion [151–153]. Whether there is an increased risk of viral or bacterial gastroenteritis in patients receiving gastric-acid-suppression therapy remains controversial [154]. Neal and coworkers [155, 156] performed a case-control study that found omeprazole treatment in the month before infection to be associated with a 10-fold increased risk of *Campylobacter* infection. Canani et al. [157] also investigated the frequency of gastroenteritis among children on gastric-acid-suppression therapy. They showed that subjects using acid-suppressing drugs were more likely to have acute gastroenteritis (OR 3.58; CI 1.87–6.86) than matched controls. No differences were observed between H_2 blocker and PPI users in acute gastroenteritis.

Small Intestine

Gastric surgery is associated with increased rates of intestinal infections. The first report on salmonellosis following gastric surgery was of 9 cases of *S. enterica t.* infection published in the *New England Journal of Medicine* in 1956 [158]. A larger study comparing 277 patients with salmonella infection with 436 patients admitted to an infectious disease hospital suffering from other infections revealed a significantly higher number of cases of gastric surgery in the salmonella-infected group than in the control group. This was confirmed by a case-control study of laboratory-confirmed patients with a *S. enterica* infection with well-matched controls. Use of both H_2 antagonists and PPIs were associated with a 4-fold increased risk of endemic *S. enterica enteritidis* infection. PPIs were also linked to an 8-fold risk of endemic *S. enterica t.* infection; however, colonization with these bacteria had no clear clinical consequences [160]. A retrospective case-control study found an increased risk of *Clostridium difficile* diarrhea under current use of PPI therapy [161]. Similar results were obtained in a case-control study using a United Kingdom clinical research database. Exposure to a PPI in the 90 days before the index date of the study was associated with a 2- to 3-fold increased risk of *C. difficile*-associated diarrhea [162–164].

With respect to *Campylobacter jejuni* infection, no association with acid suppression in a large prospective case-control study has been shown. Of the risk factors foreign travel, living on a farm, taking antibiotics or antacids, and having problems with rodents or houseflies in the home, only living on a farm was associated with illness (OR 2.484; 95% CI 1.041–5.930) [165].

Summary

There has been growing attention to effects of acid-suppression therapy on gastric microbiology: gastric acid suppression leads to a quantitative increase and change of the gastric flora dependent on length and extent of acid suppression, which seems not to be translated into symptoms or changes in small intestinal absorptive function. However, there is growing evidence for an increased risk of bowel infection in states of chronic gastric acid suppression that may influence treatment decisions in certain situations.

Gastric Acid and Hunger, Satiation and Mood

Central and Peripheral Control of Gastric Secretion

The central nervous system has an important role in the regulation of gastric acid in primates. Sham feeding studies show that up to 50% of gastric acid secretion occurs during the cephalic phase of feeding [166]. This effect is mediated primarily by the vagus nerve directly or indirectly via release of various peptide hormones. The prosecretory influence of the central nervous system on gastric acid secretion is effectively blocked by sub-diaphragmatic vagotomy. Interestingly it was demonstrated that, in addition to well-known peptide hormones such as gastrin and somatostatin, recently discovered peptides such as ghrelin also modulate acid secretion [43]. The main source of gastrin and ghrelin is the gastric mucosa [167, 168]; however, both are also produced by the hypothalamus [34, 169].

Interaction between Control of Gastric Secretion and Feeding Behavior

Gastrin tends to reduce feeding behavior in animal models [170], whereas ghrelin stimulates hunger and increases nutrient intake in various species [171], including humans [172]. Considered together these observations raise the question whether mechanisms that control gas-

tric acid secretion have a direct influence on hunger, satiety and feeding behavior and thus on body weight. Moreover, given the close anatomical relationship of feeding centers and emotional centers in the hypothalamus and limbic system, it could be envisaged that modulating gastric acid secretion could have effects on emotional well-being. Information concerning these possibilities is very limited. Campbell et al. [170] investigated the effects of proton pump (H^+/K^+-ATPase) inhibition by omeprazole on feeding behavior in hens. In addition to reduced gastric acid secretion, a reduction in energy intake was also observed. In these animal experiments, the reduction in feeding was attributed to the rise in gastrin levels with PPI inhibition by omeprazole [170]. Surprisingly, no similar experiments or observations have been reported in humans. What is established in humans is that underweight, malnourished patients have low levels of gastric acid secretion, whereas obese patients have a raised maximal secretory capacity (peak acid output) but normal basal acid output [117, 173, 174]. Studies in patients having had gastric banding surgery for morbid obesity have shown that peak acid output is significantly reduced following weight loss, whereas basal acid output is unchanged [175]. Together these observations suggest a link between body weight and acid secretion. Severe malnutrition is associated with parietal cell dysfunction, which may be the decisive control mechanism by which nutritional state influences gastric acid secretion. These findings provide interesting insights into the effect of feeding behavior, body weight, changes in body weight and gastric acid secretion. Nevertheless, despite the large number of clinical trials that involve PPIs, there is no clear link between gastric acid inhibition and feeding behavior or body weight. This could be due to the interaction between gastric acid production reflux symptoms and feeding behavior (e.g., reducing gastric acid production increases gastrin, which might inhibit food intake but reduces reflux symptoms that could well increase food intake).

Gastric Secretion and Psychological State

A related question is whether the presence or absence of gastric acid has a meaningful effect on mood or emotional state. Possible models that could help address this question include the study of conditions that are linked to reduced gastric acid secretion (atrophic gastritis, vagotomy, PPI therapy) and those in which gastric acid secretion is increased (Zollinger-Ellison syndrome, peptic diseases of the upper GI tract). Before the discovery of *H. pylori,* a number of attempts were made to establish a link between personality or emotional affect and peptic ulceration [176]. It was proposed that an elevated level of anxiety in patients with duodenal ulceration could lead to increased gastric acid production [177]. However, it was shown that although neuropsychological factors such as fear, stress and conflict did have effects on gastric acid production in healthy volunteers, the hypergastrinemia in peptic ulcer disease was independent of emotional state [178]. Moreover, it is possible that the characteristic 'ulcer personality' described in the literature is an effect rather than a cause of the disease [179]. New investigations in patients with GERD have revealed a further aspect of the relationship between stress, GI symptoms and disease: stress increases visceral sensitivity and the association between reflux events and symptoms [180]. On this basis it has been shown that symptoms associated with GERD can be reduced by relaxation training [181]. However, external stressors do not increase acute gastric acid secretion [182].

Very little data exist regarding the central perception of gastric acid and influence on affect or mood. Kern et al. [183] were able to show that, even below the conscious perception threshold, esophageal acid exposure leads to a rapid and intense cortical activation in GERD patients and healthy volunteers. This raises the question of how a potentially painful stimulus such as acid is perceived in gastrointestinal disease. Centrally active mediators that may play a role in this process include corticotropine-releasing hormone, 5-HT_3-receptor-ligands, melatonin und dopamine [184–187], all of which are thought to play a role not only in the response to pain and other stressful stimuli but also in psychological state. Epidemiological studies provide further evidence of the link between affective disorders and changes in gastric acid secretion and peptic ulcer disease: a Canadian study revealed that patients receiving antidepressant therapy had an increased usage of PPIs [188]. Moreover, a high percentage of patients with bipolar disorder have circulating anti-parietal antibodies [189]; however, it remains unclear whether these patients also have atrophic gastritis or hyposecretion of gastric acid.

Summary

There is little evidence for involvement of gastric acid or its suppression in sensation of hunger, satiation or mood. In animal models caloric intake was shown to be reduced under acid-suppression therapy; however, no clear link between acid suppression and changes in feeding behavior or body weight has been established. Gastric acid production may be acutely increased by neuropsy-

chological factors such as anxiety or fear; however, in peptic ulcer disease it is independent of the emotional state. The characteristic 'ulcer personality' described in the literature may therefore be an effect rather than a cause of the disease. Future directions of studies will include not only the effects of gastric acid secretion on perception, mood and emotion, but also whether anti-secretory therapy has effects on central processes and how these are mediated. Early evidence that supports central effects of these medications suggest direct central anticonvulsive and anti-tussive effects for PPIs [190, 191].

Conclusion

Gastric acid plays a role in regulating gastric function, protects against GI pathogens, facilitates the digestion and absorption of certain nutrients and may modulate feeding behavior. These properties represent a clear advantage to individuals on the verge of starvation who need to extract every last nutrient from a limited, contaminated food supply in order to survive. This is the situation in which most humans existed until the very recent past and it continues to be the case in many individuals living in the developing world; however, it is only now becoming clear to what extent gastric acid has clinically relevant effects in the developed world. Although the absolute risk is low, acid suppression does increase the risk of GI infection and this may be of importance in community outbreaks, and especially in hospitals and nursing homes in the light of increasing virulence of bacterial strains such as *C. difficile*. Similarly, recent evidence suggests that the effect of acid suppression on calcium absorption increases the risk of hip fracture in at-risk populations. Long-term follow-up has not found evidence that potent acid suppression with PPIs is related to increasing rates of esophageal cancer or other malignant diseases; however, this needs to be monitored as patients embark on an essentially life-long therapy with these medications. Finally a better understanding of neuropsychological effects of gastric acid is required. The link between gastrointestinal 'humors', health and well-being has a history stretching back to Galen, and there surely is more to be understood about the way gastric acid affects GI function, feeding behavior and mood.

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