Physiology of acid secretion

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Gastric acid secretion

• Important non-immunological first line of defence against ingested bacteria
• Ability to produce acid allowed vertebrates to ingest more complex diets but also protected them against microbes that gained access through the GI tract
Important historical figures in the acid story

**Pioneers**: Beaumont, Prout, Pavlov, Edkins, Popielsky, Kowalewski, Kay
Regulation of gastric acid secretion

• Finely controlled process dependent on overlapping neural, hormonal and paracrine pathways.
• This ensures production of the optimal amount of acid
• Too little acid: problems with absorption of iron, calcium, B12 and some drugs
• Too much: oesophageal, gastric and duodenal injury
The gastric mucosal barrier: why does the stomach not digest itself??

- Surface mucous cells produce a thick alkaline-rich layer of mucus
- Secretion of bicarbonate
- High polarity of surface epithelial cells
- Tight junctions between adjacent epithelial cells
- Abundant blood flow
- All these factors combine to produce and maintain a protective blanket 200-300µm thick
Regulation of gastric acid secretion

• The human stomach has an intricate submucosal plexus that secretes a variety of transmitters including nitric oxide, vasoactive intestinal peptide (VIP), gastrin releasing peptide (GRP), substance P & calcitonin gene-related peptide (cGRP).

• The gastric mucosa contains specialised cells that secrete several important substances including histamine, gastrin, somatostatin, HCl, pepsinogens, mucin, intrinsic factor, leptin and ghrelin.
Gastric gland

- Gastric pit
- Surface mucous cell
- Mucous neck cell
- Parietal cell
- Chief cell
Cell lineage

S. Karam et al
• Binding of secretagogues to parietal cells induces changes in second messengers that regulate the translocation and activation of the H⁺/K⁺ ATPase pump.
• Upon stimulation of parietal cells, the pumps are translocated from the cytoplasmic tubulovesicles into the membrane of the secretory canaliculus, forming the microvilli lining the canalicular space.
H⁺/K⁺ ATPase pump

- Involved in the final stages of acid secretion. Stimulated by signals from H₂, muscarinic (M3) and gastric receptors.
- Transports its cations as a cycle of phosphorylation and dephosphorylation of the transport protein.
- A KCl pathway is activated and the net result is pumping of hydronium ions (H₃O⁺) at a concentration of 160mM (pH 0.8), equivalent to a 4 million-fold gradient across the surface of the parietal cell.
Phases of Gastric Acid Secretion

CEPHALIC
Sight
Smell
Taste
Thought

GASTRIC
Antral distention
Protein content
↑ pH (>4)

INTESTINAL
Intestinal gastrin
Absorbed amino acids

Increased circulating gastrin

Decreased intragastric pH

Increased H⁺ secretion

Gastric phase
Intestinal phase

- Nervous Mechanisms
- Hormonal Mechanisms
Control of acid secretion
Helicobacter pylori exerts a major influence on the physiology of gastric acid secretion
H. pylori in the stomach
Effect of *H. pylori* on basal gastrin levels

El-Omar et al Gastroenterology 1995
Effect of *H. pylori* on gastric acid secretion

El-Omar et al Gastroenterology 1995
Chronic *H. pylori* infection

**Duodenal ulcer phenotype**
- Around 10-15% of infected subjects
- Antral predominant Gastritis
- High gastrin and acid secretion
- Impaired inhibitory control of acid secretion
- Protection from gastric cancer

**Simple gastritis phenotype**
- Majority of infected subjects
- Mild mixed gastritis
- High gastrin but normal acid secretion
- No gastric atrophy
- No significant clinical outcome

**Gastric cancer phenotype**
- Around 1% of infected subjects
- Corpus-predominant gastritis
- Multi-focal atrophic gastritis
- High gastrin
- Hypo/achlorhydria
- Low pepsinogen I and pepsinogen I/II ratio
- Increased risk of gastric cancer

Amieva & El-Omar, Gastroenterology, in press
Pathophysiology of duodenal ulcer disease

↑ duodenal acid load
- Decreased HCO$_3^-$
  → gastric metaplasia
  → HP colonisation
  → ulceration

↑ gastrin release
- Caused by ↓ somatostatin
  CagA+ve > CagA-ve

↑ acid response to gastrin

↑ parietal cell mass
- Sensitivity unimpaired because of absence of corpus gastritis

↑ gastric metaplasia
→ HP colonisation
→ ulceration
Eradication of *H. pylori* Infection in DU Patients

**DUODENUM**
- Decreased acid load & increased bicarbonate

**CORPUS**
- Cure of gastritis
- Reduction in acid secretion

**ANTRUM**
- Cure of gastritis
- Normalisation of gastrin & somatostatin
Divergent Responses to *H. pylori* Infection

Chronic *H. pylori* Infection

- **Antral predominant Gastritis**
  - Acid, little or no atrophy
  - Low risk of gastric ca

- **Corpus predominant Gastritis**
  - Acid, gastric atrophy
  - High risk of gastric ca

**Mild Mixed Gastritis**

- **Normal Acid**

- **DU disease**

- **No significant disease**

- **Gastric Ca**

?

* Bacterial ? Environment ? Host
Gastric cancer

- Global killer, 2nd commonest cause of cancer death
- Retains a very poor prognosis in the West
- Major advance in understanding the pathogenesis came with discovery of *H. pylori* infection
Pathological evolution of gastric cancer: Multi-stage process of carcinogenesis “Correa Model”

**Normal mucosa** $\rightarrow$ **Chronic gastritis** $\rightarrow$ **Atrophic gastritis** $\rightarrow$ **Intestinal metaplasia** $\rightarrow$ **Gastric dysplasia**

**Early stages**
- Inflammation
- Increased proliferation
- Increased apoptosis
  - Atrophy
  - Achlorhydria
- Bacterial overgrowth

**Late stages**
- Accumulation of genetic changes
- Loss of growth control
- Decreased apoptosis
- Invasion and metastasis

**Inflammation** $\rightarrow$ **Loss of parietal cells** $\rightarrow$ **Stem cell amplification**

*Helicobacter pylori*
The gastric cancer phenotype

• Severe inflammation
• corpus predominant pattern
• gastric atrophy
• Hypo/achlorhydria
• Bacterial overgrowth
**Table 2. The Development of Gastric Cancer in H. pylori–Positive Patients According to Abnormalities at Base Line.**

<table>
<thead>
<tr>
<th>Abnormalities at Base Line</th>
<th>All H. pylori–Positive Patients (N=1246)</th>
<th>H. pylori–Positive Patients with Gastric Cancer (N=30)</th>
<th>Relative Risk (95% CI)*</th>
<th>H. pylori–Positive Patients with Intestinal-Type Cancer (N=23)</th>
<th>H. pylori–Positive Patients with Diffuse-Type Cancer (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>no. (%)</td>
<td></td>
<td>no.</td>
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<td>Grade of atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>None or mild†</td>
<td>381</td>
<td>3 (0.8)</td>
<td>1.0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Moderate</td>
<td>657</td>
<td>18 (2.7)</td>
<td>1.7 (0.8–3.7)</td>
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<tr>
<td>Severe</td>
<td>208</td>
<td>15 (7.2)</td>
<td>4.9 (2.8–19.2)</td>
<td>14</td>
<td>1</td>
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<tr>
<td>Distribution of gastritis</td>
<td></td>
<td></td>
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<tr>
<td>Antrum predominant†</td>
<td>699</td>
<td>2 (0.3)</td>
<td>1.0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Panantrum</td>
<td>337</td>
<td>14 (4.2)</td>
<td>15.6 (6.5–36.8)</td>
<td>4</td>
<td>10</td>
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<tr>
<td>Corpus predominant</td>
<td>210</td>
<td>20 (9.5)</td>
<td>34.5 (7.1–166.7)</td>
<td>19</td>
<td>1</td>
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<tr>
<td>Intestinal metaplasia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Absent†</td>
<td>782</td>
<td>6 (0.8)</td>
<td>1.0</td>
<td>1</td>
<td>5</td>
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<tr>
<td>Present</td>
<td>464</td>
<td>30 (6.5)</td>
<td>6.4 (2.6–16.1)</td>
<td>22</td>
<td>8</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.
†Patients in this category served as the reference group.
Effect of pH on intragastric bacteria

Intragastric pH 1.5

Intragastric pH 7
### Host genetic factors
- *IL-1B*-511*T
- *IL-1-RN*-2*2
- *IL-10* ATA haplotype
- *TNF-A*-308*A
- *IL-8*-251*A
- *TLR4*-896*G
- *MBL2* HYD haplotype

### Bacterial virulence factors
- cagA PAI
- *vac A s1/m1*

### Environmental factors
- Smoking
- Poor diet

### Gastric cancer phenotype
- Corpus-predominant gastritis
- Multi-focal atrophic gastritis
- High gastrin + Hypochlorhydria
- Low pepsinogen I and pepsinogen I/II ratio
- Bacterial overgrowth causing inflammation
- Increased risk of gastric cancer
Candidate genes

- Pro-inflammatory
- Relevant to *H. pylori* infection
- Central role in gastric acid physiology
- Polymorphic gene with functionally relevant genetic variants that are frequent in the population
- *IL-1B* (encoding IL-1β)
Interleukin-1 Beta

• Important pro-inflammatory cytokine
• Up-regulated by *H. pylori* infection
• Most powerful gastric acid inhibitor known

• **Interleukin-1 cluster:** *IL-1B*, and *IL-1RN*
• **Gene polymorphisms:**
  *IL-1B*: C-T transitions at -511T+, -31C+
  *IL-1RN*: penta-allelic 86 bp VNTR in intron 2 allele 2 associated with inflammatory conditions
## Role of composite pro-inflammatory polymorphisms on risk of non-cardia gastric cancer

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Non-cardia gastric cancer (N=188)</th>
<th>Controls (N=210)</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Odds ratio</td>
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<tr>
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<td>3-4</td>
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<td>27.3</td>
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</tbody>
</table>

Pro-inflammatory polymorphisms: *IL-1B*-31/-511*2, *IL-1RN*2/*2
*TNF-A*-308*2, *IL-10* ATA/ATA

**H⁺/K⁺-ATPase-IL-1β transgenic mice**

Path findings:
- Large stomachs
- Large spleens
- Altered T and NK cell numbers

*Courtesy of Dr Timothy Wang: personal communication*
H\(^+/K^+\)-ATPase-IL-1\(\beta\) transgenic mice progress to atrophy, severe dysplasia and cancer.

Courtesy of Dr Tim Wang
H+/K+-ATPase-IL-1β transgenic mice

- Produce high IL-1 β in gastric tissue
- Achlorhydric
- Progress to atrophy, severe dysplasia and cancer
- Process accelerated by *H. felis* infection
- First example of a single cytokine transgenic gastric cancer model