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Gastric Acid in Vertebrates

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Gastric secretion of hydrochloric acid appears to be unique to vertebrates and is almost ubiquitous in all fishes, amphibians, reptiles, birds and mammals. Comparative anatomy and physiology suggest that gastric acid has evolved approximately 350 million years ago. The similarity of the acid-secreting mechanism across all classes of vertebrates implies a major advantage for selection, but the evidence regarding its precise purpose remains inconclusive.

Key words: Achlorhydria; Amphibians; birds; evolution; fishes; gastric acid; gastric mucosa; mammals; pepsin; reptiles

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EVOLUTION

The acid-secreting stomach in vertebrates

There is no direct evidence from fossils on the development of the acid-secreting stomach. Fossils are usually not even preserved well enough to allow anatomical recognition of internal organs including the stomach. Thus, the development of the acid-secreting stomach in vertebrates must be inferred from comparative anatomy and comparative physiology. It is likely from this that present-day animals and their fossilized ancestors have similar gastric functions.

The evolution of the earliest chordate animals probably started approximately 450 million years ago with the development of Acrania and Agnata (Fig. 1). Present-day 'survivors' of these archaic fish are lancelets and lampreys. Both groups are stomachless and are not secreting hydrochloric acid of any sizable concentration in their gastrointestinal tract. A stomach with acid secretion is probably found for the first time in the elasmobranchs (sharks and rays), dating back approximately 350 million years (1–3). Since then, with very few exceptions, acidic stomachs have been ubiquitous in all higher vertebrates, including amphibians, reptiles, birds and mammals.

Stomachless vertebrates

A true stomach is an enlargement of the lumen of the proximal gastrointestinal tract with a sphincter-like structure at its distal end (4). Stomachless fish occur in the earliest and in the most recent (teleost) classes. All members of the lowest class of chordate animals, i.e. cyclostomes (lampreys and hagfish), have no stomach.

Among later vertebrates, stomachless species are rare

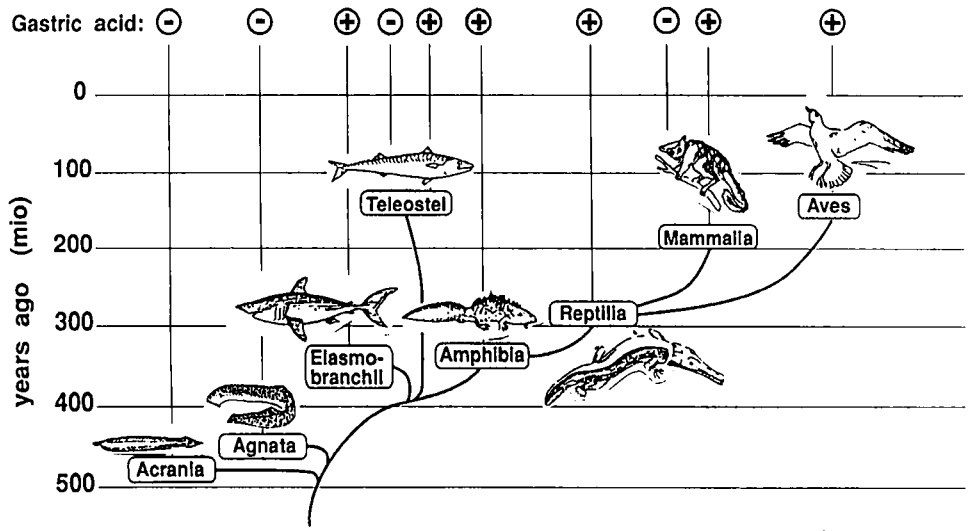


Fig. 1. Scheme of evolution of vertebrates. Vertical lines indicate, presence (+) or absence (−) of a true stomach and gastric acidity in present-day animals.

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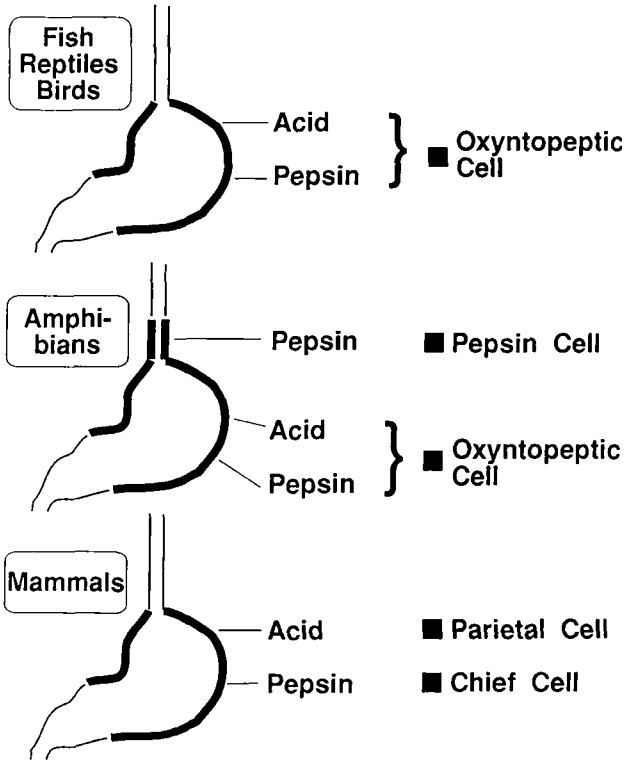


Fig. 2. Distribution of acid and pepsinogen secreting mucosal cells in the stomach of vertebrates. A primate-like stomach is drawn for all examples, to facilitate comparison.

exceptions. The lack of a stomach in some teleosts, especially in the families of Cyprinidae (e.g. carps) and Labridae (e.g. wrasses) is probably secondary, because most other teleosts and evolutionary much earlier fishes possess a stomach (1).

It is remarkable that there are only two known land-living vertebrates without an acidic stomach in adult life. In general, the presence of a stomach is associated with gastric secretion of hydrochloric acid and pepsinogen. The only known exceptions of this rule are egg-laying mammals (monotremes), i.e. the spiny anteater (Echidna) and the duck-billed platypus, strange animals also with respect to other characteristics. They do have a stomach, but it is entirely lined with stratified squamous epithelium and consequently lacks gastric acid (5–7). A well-known example of a transient 'physiological achlorhydria' is the gastric brooding frog *Rheobatrachus silus* from Australia, where the female swallows the eggs and broods its young in the stomach. Gastric acid secretion is inhibited during this time probably by prostaglandin E_2 secreted by the larvae (8, 9).

It is not clear how some vertebrates can 'afford' to be agastric since no common characteristic of stomachless animals has been identified. Many hypotheses have been forwarded, but none appears to be convincing (10). It is likely that a stomach as a food reservoir is not needed in fishes with triturating feeding habits, but is beneficial in macrophagous animals. This explains the lack of a stomach in Agnatha and Acranii. The ontogenesis of tailless amphibians (Anura), but not of salamanders and newts (Urodeles), appear to follow the same rule: a stomach is absent (and presumably not needed) as long as the tadpoles feed on algae and similar small food particles. It develops only at the time when the hind legs appear. This may be interpreted as a preparation for taking large prey in adult life when they swallow it whole (11).

The absence of a stomach is usually associated with microphageous behavior and with well developed pharyngeal teeth for trituration of food. But this correlation of lack of a stomach and microphageous behavior and feeding habits is not universal: some agastric teleosts feed on algae while others prefer crustaceans and molluscs (1). Thus, either gastric acidity is less important than implied by its wide distribution, or achlorhydric vertebrates own some (unknown) mechanisms that compensate for this defect.

Proton gradient

In mammals, the proton gradient from blood (pH 7.4) to the gastric lumen (pH 0.8) amounts to 1 to 2.5×10^6 and thus represents the largest known ion gradient in vertebrate physiology. It is remarkable that pH measurements in stomachs of all other classes of vertebrates gave similar results, ranging between 0.8 and 2.0 in sharks, rays, crocodiles, lizards, tortoises, and various birds (2–4). It is therefore likely that the gastric proton pump, the H^+K^+-ATPase, is similar in all acid-producing vertebrates.

Acid-secreting mucosa

Keeping with a conservative evolution, the acid-secreting area is found adjacent to the squamous epithelium of the esophagus, forestomach or rumen in all vertebrates (12, 13) (Fig. 2). In non-mammalian vertebrates, the acid-secreting cells also synthesize and secrete pepsinogen and are therefore referred to as oxyntopeptic cells. As a particularity of amphibians, pure peptic cells are located in the mucosa of the lower esophagus. A separation of the two functions of oxyntopeptic cells into parietal cells and chief cells is found in mammals only. Unique among acid-secreting cells is the secretory or intracellular canaliculus of the parietal cell which may render acid secretion more efficient (13, 14).

PURPOSE OF GASTRIC ACID

The existence of gastric acid secretion since presumably several hundred million years and its almost ubiquitous distribution among present-day vertebrates indicates a major advantage for selection. This wide distribution alone suggests an important role of gastric acid, because useless organs and functions would most likely be eliminated by evolution over large time scales. However, the evidence regarding the precise mechanism is inconclusive.

In a classical view, gastric acidity prevents infections, activates pepsinogen and thus initiates protein digestion. In

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addition, it is thought to facilitate absorption of iron, calcium and cobalamin.

Protein denaturation and digestion

It is conceivable that gastric acid has some function for denaturating proteins before they reach the small intestine where they may be absorbed intact and act as antigens to produce allergic reactions. It has been shown in many mammalian species that gastric acidity is high before birth and decreases markedly during the early neonatal period. This, together with low activity of pancreatic enzymes and the ability of the neonatal intestine to absorb intact proteins, allows antibodies to be transferred from the mother milk to the suckling. In humans, however, the majority of immune globulins reaches the fetus across the placenta (15).

Data concerning the role of gastric acid and peptic digestion for protein assimilation indicate a minor importance (16). In humans, protein digestion by the stomach does not appear to be impaired by achlorhydria. Even in patients with total gastrectomy, most metabolic consequences can be attributed to malnutrition rather than to malabsorption (17).

Disinfection mechanism

A chemical disinfectant mechanism such as hydrochloric acid at the upper end of the gastrointestinal tract appears beneficial, especially if normal emptying of a full stomach takes several days as it has been shown for many fish species (14). This is the most popular explanation for the need of strong gastric acid (18–20). Hydrochloric acid at a pH below 3 is bactericidal in vitro to many pathogenic intestinal bacteria such as *Campylobacter jejuni*, *Yersinia enterocolitica*, *Salmonella* ssp. and *Shigella* ssp. It is clear from clinical and epidemiological studies that low or absent acid secretion predisposes for cholera in man (21–23). It is also likely that the risk to acquire salmonelloses is higher in persons with reduced gastric acidity (24, 25), whereas this is less clear for other enteric infections such as shigellosis (26), brucellosis (27), giardiasis (28), strongyloidiasis, pseudomebranous colitis due to *Clostridium difficile* and infestation with *Diphyllobotrium latum* (18–20). Evidence is lacking for other infections. One might even speculate that acid-fast bacteria such as Mycobacteria have developed their acid-resistance as a protective mechanism against hydrochloric acid of vertebrates.

The food in Western countries is clean, nearly sterile. This may permit even profound inhibition of gastric acidity without any apparent increase of the incidence of gastrointestinal infections. It should be emphasized, however, that profound reduction of gastric acidity may have more severe consequences in third-world countries, but meaningful data are not yet available.

Absorption of iron

Gastric acid is believed to be important for iron absorption. Most dietary iron from plant sources consists of trivalent (ferric) salts which form insoluble compounds at a pH >3 (29) unless the formation of macromolecules with hydroxyl groups is prevented by chelation (30). In contrast, most divalent (ferrous) iron remains in solution at pH 8.

On the other hand, organic iron, in particular in the form of hemoglobin or myoglobin, is readily absorbed in the absence of gastric acid (31). Therefore, with respect to iron absorption, gastric acidity seems to be important for strict vegetarians only.

Absorption of calcium

Vertebrates may be considered to be in a special need to absorb large quantities of calcium because of their calcium requirement to build bones. The argument appears weak, however, because a similar calcium uptake is probably needed in stomachless vertebrates. Also, non-vertebrate animals need calcium, such as shellfish, for building an external and cuttlefish an internal shell.

The most common calcium source, calcium carbonate, is barely soluble in neutral water and should therefore not be readily available for absorption by the small intestine. The problem may be overcome by dissolution in the acidic gastric pH where it forms soluble calcium chloride that can be absorbed in the small intestine (32).

The role of gastric acidity in calcium absorption has been studied in man, but the results are controversial (33). Calcium carbonate, the most widely found form of calcium, has been shown to be absorbed to more than 20% in normal volunteers as compared to less than 5% in achlorhydric individuals, whereas calcium citrate was not influenced (34). A reduction in the absorption of calcium carbonate, however, was found only if it was given into an empty achlorhydric stomach and not if given in a more physiological way together with a meal (34). Furthermore, in another study, using an isotopic method rather than a gastrointestinal lavage technique, absorption of calcium citrate, calcium carbonate or calcium in cheese products was similar in untreated volunteers (gastric pH 3.0) or treated with cimetidine (gastric pH 7.4) and in one person with achlorhydria (35). This rather unexpected finding was explained by slightly acidic secretions of the small intestinal mucosa, by proton adsorption to the intestinal cells due to fixed negative surface charges, or by solubilization of calcium carbonate in bile or pancreatic juice (35).

Intake of phytates (36, 37) and dietary fibre (38, 39) have been associated with low calcium availability. However, calcium malabsorption becomes relevant only if at least the same amount (weight by weight) of phytates as calcium is eaten together (36, 37). On the other hand, it is not clear whether this effect may be enhanced in the absence of gastric acid.

Absorption of cobalamin

In man, the only indispensable function of the stomach is synthesis and secretion of intrinsic factor. Although intrinsic

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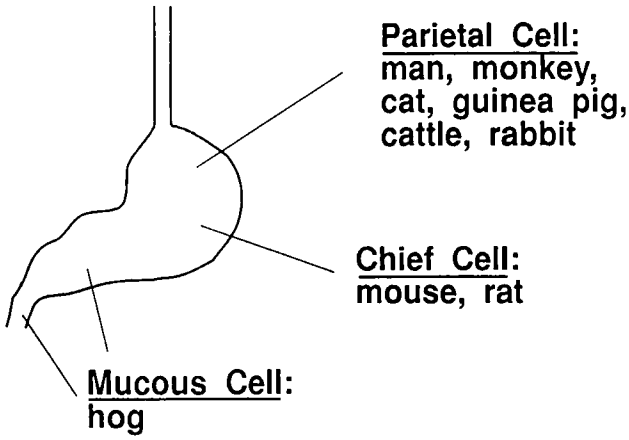


Fig. 3. Localization of synthesis and secretion of intrinsic factor in different mammals.

factor is provided by the parietal cell in man and some other mammals such as apes, cats, guinea pigs, cattle and rabbits, the regulation of secretion is different from that of acid (40). For example, subtotal inhibition of basal and histamine-stimulated acid secretion by omeprazole does not affect secretion of intrinsic factor (41). Furthermore the association of intrinsic factor with acid in the parietal cell appears rather incidental because intrinsic factor is provided by chief cells in rats and mice, and by mucous cells in pigs (40) (Fig. 3). Nevertheless, another connection between gastric acid and cobalamin seems to be physiologically important. While cimetidine, ranitidine and omeprazole decrease basal and stimulated acid secretion, secretion of intrinsic factor was unchanged in most, but not all studies (for review see Ref. 42). Similarly, absorption of crystalline cobalamin was normal during treatment with secretory inhibitors (42–44). In contrast, absorption of protein- bound cobalamin was markedly reduced during inhibition of acid secretion, suggesting that gastric acid is important for releasing cobalamin from dietary protein before binding to 'R' proteins and intrinsic factor (42–44). Addition of exogenous acid in the form of a dietary cranberry drink improved absorption of protein-bound cobalamin (44). Malabsorption of cobalamin may therefore be of concern in the long-term treatment with strong acid inhibitors.

Thus, the connection between gastric acid and cobalamin is less tight than usually expected. Even within various mammals, the occurrence of intrinsic factor in different gastric and duodenal cells (Fig. 3) indicates a less 'conservative' evolution than that of acid secretion. This is further underlined by the fact that among ten known congenital defects in the absorption and transport of cobalamin absorption described in man, none is associated with lack of gastric acid secretion (45, 46). In addition, congenital achlorhydria has probably never been reported in the medical literature.

Protection against gastric carcinogenesis

Achlorhydria as a final stage of atrophic gastritis is an accepted risk factor for the development of gastric adenocarcinoma (47–49). From an evolutionary point of view, the protective role of gastric acid is probably of minor importance, because the relative risk for gastric cancer between humans with and without achlorhydria is small and carcinogenesis takes too long to be relevant for selection.

DISADVANTAGES OF GASTRIC ACID SECRETION

Gastroenterologists usually see gastric acid as a pathogenic factor for acid-related diseases rather than a life-saving mechanism. It may well be that in vertebrates other than modern civilized man the advantages of acid surpass the disadvantages by far.

In the pathogenesis of peptic ulcer disease and gastroesophageal reflux disease, it seems likely that gastric acid is harmful only if additional factors are present. For peptic ulcer disease, either *Helicobacter pylori* or non-steroidal anti-inflammatory drugs are almost always needed. *H. pylori* may be confined to modern man, and antirheumatic drugs are products of modern civilisation. Since gastroesophageal reflux disease has an almost negligible mortality, this disease may not be relevant for selection. In addition, hiatus hernia as a 'permissive' factor for reflux disease may be confined to westerly-civilized man (50).

CONCLUSIONS

The evolutionary preservation of gastric acid for probably several hundred million years despite the risk of acid related diseases in virtually all contemporary vertebrates indicates a major advantage for selection, but the exact role remains unknown. One of the likely tasks of acid is a defence against pathogenic enteric bacteria under poor sanitary conditions.

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