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Review

Acid-sensing ion channels in gastrointestinal function

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ABSTRACT

Gastric acid is of paramount importance for digestion and protection from pathogens but, at the same time, is a threat to the integrity of the mucosa in the upper gastrointestinal tract and may give rise to pain if inflammation or ulceration ensues. Luminal acidity in the colon is determined by lactate production and microbial transformation of carbohydrates to short chain fatty acids as well as formation of ammonia. The pH in the oesophagus, stomach and intestine is surveyed by a network of acid sensors among which acid-sensing ion channels (ASICs) and acid-sensitive members of transient receptor potential ion channels take a special place. In the gut, ASICs (ASIC1, ASIC2, ASIC3) are primarily expressed by the peripheral axons of vagal and spinal afferent neurons and are responsible for distinct proton-gated currents in these neurons. ASICs survey moderate decreases in extracellular pH and through these properties contribute to a protective blood flow increase in the face of mucosal acid challenge. Importantly, experimental studies provide increasing evidence that ASICs contribute to gastric acid hypersensitivity and pain under conditions of gastritis and peptic ulceration but also participate in colonic hypersensitivity to mechanical stimuli (distension) under conditions of irritation that are not necessarily associated with overt inflammation. These functional implications and their upregulation by inflammatory and non-inflammatory pathologies make ASICs potential targets to manage visceral hypersensitivity and pain associated with functional gastrointestinal disorders.

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1. Luminal acidity and tissue acidosis in the gastrointestinal tract

Acid is of paramount relevance to digestion. Being one of the prime secretory products of the stomach, hydrochloric acid (HCl) not only promotes digestion (Holzer, 2011a) but also protects the gastrointestinal tract from potentially infectious microorganisms that may be ingested with food (Canani and Terrin, 2010). The parietal cells in the gastric mucosal glands are the most productive source of acid in the body. Equipped with the so-called proton pump, these cells can secrete HCl to build up a luminal H^+ concentration that – with an average diurnal pH of 1.5 – is 6 orders of magnitude higher than in the gastric lamina propria (Holzer, 2007a, 2011). The physiological functions of gastric acid comprise the conversion of pepsinogen to pepsin, solubilisation of food components, digestion and absorption of several nutrients, and elimination of ingested pathogens (Pohl et al., 2008), At the same time, the high luminal concentration of HCl endangers the integrity of the mucosa in the stomach and adjacent regions of the gastrointestinal tract. The injurious threat that HCl exerts on the mucosa is kept in check by a network of mucosal defence mechanisms and by the lower oesophageal and pyloric sphincters which control the backflux and propulsion of the acidified gastric juice (Holzer, 2007b). In order to regulate these defence systems according to need, cells that are able to sense acid are required, among which epithelial cells and acid-sensitive neurons play a particular role. Following activation by a drop of extracellular pH, these cells evoke both local and remote homeostatic reactions (Fig. 1). When the surveillance and/or defence systems are defective, acid-related diseases including gastro-oesophageal reflux disease, dyspepsia, gastritis and gastroduodenal ulcer disease may ensue.

Deviations from the physiological value of extracellular pH (7.4) occur not only in the lumen of the upper gastrointestinal tract but can be observed throughout the gut including the small and large intestine. The luminal pH profile along the digestive system of healthy subjects exhibits a distinct shape (Fallingborg, 1999; Nugent et al., 2001), with peaks of acidity occurring in the stomach and in the proximal large bowel. In the foregut it is primarily

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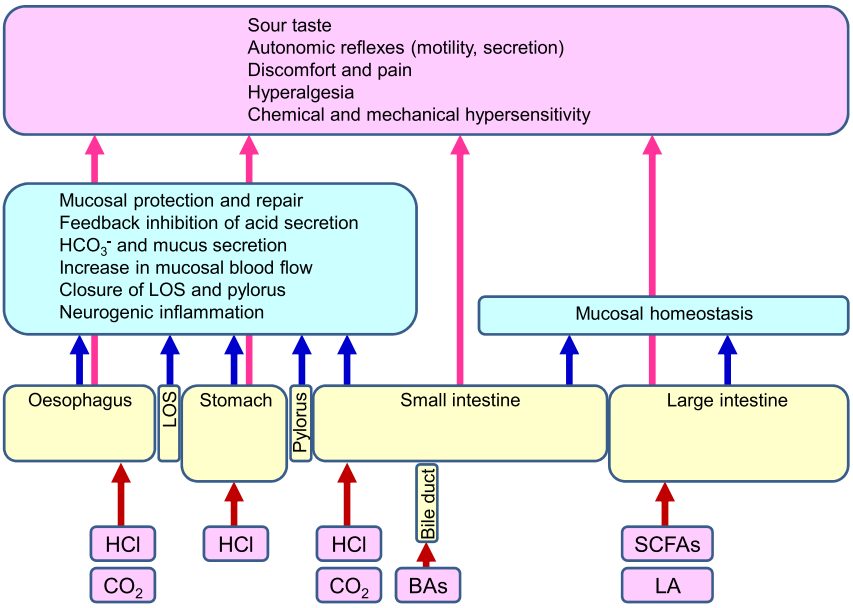

Fig. 1. Acid surveillance in various regions of the gastrointestinal tract. The graph shows various intrinsic sources of acid along the gastrointestinal tract. Acidity is monitored by epithelial cells and other cells of the gastrointestinal tract, notably intrinsic and extrinsic sensory neurons. When activated by acidification, the acid-sensing cells initiate local homeostatic reactions within the gastrointestinal tract (blue boxes) as well as remote warning reactions (pink box) in which primary afferent, cerebral and autonomic neurons are involved. BAs, bile acids; LA, lactic acid; LOS, lower oesophageal sphincter; SCFAs, short chain fatty acids (acetic, butyric and propionic acid). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

HCl and bicarbonate (HCO_3^-) secretion that determines the luminal pH, whereas in the colon it is mainly mucosal HCO_3^- and lactate production as well as microbial transformation of carbohydrates to short chain fatty acids (acetic, butyric and propionic acid) and formation of ammonia that are responsible for luminal acidity. The role which the microbiota plays in the physiological and pathophysiological regulation of acidity along the gut has not yet been fully disclosed, although it is evident that many species of the microbiota are able to generate metabolites that have a bearing on luminal acidity. Conversely, variations in luminal pH can have an impact on microbiota diversity and activity (Tana et al., 2010). Thus, acid-related diseases as well as their treatment with proton pump inhibitors have a significant effect on microbiota diversity in the oesophagus and stomach (Amir et al., 2014). The pH profile along the alimentary canal can be changed by surgical interventions, by inflammatory bowel disease (Nugent et al., 2001; Holzer, 2009) and, very likely, by alterations in the composition of the luminal microbiota.

As in other tissues, acidosis in the gastrointestinal wall can be a pathological condition that may result from excess intake of acid, excess gastric acid secretion, defective acid containment, metabolic acidosis and acidosis due to microbial activity, inflammation, ischaemia (hypoxia), malignant tumour growth and gastrointestinal motor stasis (Holzer, 2011a). Luminal acid threats as well as harmful tissue acidosis are monitored by multiple acid-sensing epithelial cells and neurons and counteracted by cellular mechanisms of acid-base regulation and systemic responses designed to maintain homeostasis. Through these measures, structural injury and functional impairment of the tissue are prevented (Holzer, 2011a).

2. Acid-evoked neurogenic inflammation and pain in the gastrointestinal tract

Krishtal and Pidoplichko (1981) were the first to observe that sensory neurons are able to react to protons in their vicinity. Since then, a plethora of studies has confirmed this discovery and shown that acid is a potent stimulator of primary afferent neurons. As reviewed by Kress and Waldmann (2006), two principal types of proton-gated inward currents in dorsal root ganglion (DRG) neurons can be distinguished. The first type is a fast and rapidly inactivating inward current carried by Na^+, which is highly sensitive to H^+ as the threshold activation occurs at a pH of 7. While this type of proton-gated current is seen in most DRG neurons, the second type is observed only in DRG neurons that are excited by capsaicin (Bevan and Geppetti, 1994). This second type of slow and non-desensitizing current is less sensitive to protons, activated only at pH levels below 6.2 (Petersen and LaMotte, 1993) and carried by Na^+, K^+ and Ca^{2+} (Zeilhofer et al., 1997). Although several acid-gated ion channels are likely to contribute, the second type of proton-activated conductance in DRG neurons shares many similarities with the acid-evoked current through the transient receptor potential channel of vanilloid type 1 (TRPV1), while the fast and rapidly inactivating proton-gated current resembles currents carried by acid-sensing ion channels (ASICs) (Waldmann et al., 1997; Kress and Waldmann, 2006).

Acid-evoked stimulation of sensory neurons in the gastrointestinal tract and other organs elicits two distinct systemic responses: local release of neuropeptides from the peripheral axons in the tissue as well as autonomic reflexes, sensation and pain (Holzer, 1988; Holzer and Maggi, 1998). By releasing peptide transmitters in the periphery, sensory nerve fibres have the capacity to regulate vascular diameter and permeability and other tissue processes, these effects being embodied in the term *neurogenic inflammation*. This efferent-like mode of operation of sensory neurons may take place independently of nociception, and it has been hypothesized that some DRG neurons are specialized in controlling peripheral effector mechanisms only, while other DRG neurons may be specialized in the afferent signalling of sensation and pain (Holzer and Maggi, 1998). The neuropeptides mediating the efferent-like mode of operation comprise, among others, calcitonin gene-related peptide (CGRP) and the tachykinins

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