PERSPECTIVES

TRiPping down the oesophagus

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The oesophagus acts as a conduit that efficiently transports swallowed food and beverages from the oropharynx to the stomach. Under physiological circumstances, passage of ingested foods or drinks is not actively perceived, but potentially harmful substances that are excessively hot, cold or large evoke painful sensations when passing down the oesophagus. A substantial portion of the adult population, however, suffers from heartburn and regurgitation induced by pathological reflux of acid, bile and other gastric contents into the oesophagus. This condition is known as gastro-oesophageal reflux disease (GERD) and afflicts up to one fifth of the Western population (Kahrilas, 2008).

Since gastric acid was recognised as the culprit for evoking GERD symptoms, many patients have benefitted from pharmacotherapy that suppresses gastric acid secretion. Nevertheless, a minority of patients, especially the ones having non-erosive reflux disease or functional heartburn, have acid suppression therapy-resistant symptoms. Hypersensitivity of the oesophagus to physiological amounts of acid reflux and/or hypersensitivity to mechanical or thermal stimuli may contribute to these patients' symptoms.

Sensory signals originating in the oesophagus are conveyed to the central nervous system by two distinct pathways. Nodose ganglion neurons receive afferent fibres running in the vagal nerves and project to the nucleus of the solitary tract, whereas cervical and thoracic dorsal root ganglion neurons conduct information from oesophageal spinal nerves to the dorsal horn of the spinal cord. This latter pathway is considered the most important one for integration of nociceptive signals (Miwa *et al.* 2010).

Currently there is great interest in the cellular receptors that convert noxious chemical, mechanical and thermal stimuli into action potentials. These receptors are essential for understanding oesophageal sensation and can be targeted in treatments of oesophageal hypersensitivity. As such transient receptor potential channel vanilloid 1 (TRPV1) and to a lesser extent acid-sensing ion channels (ASIC 1–3) have already been identified as oesophageal detectors of acid stimuli (Miwa *et al.* 2010).

In this issue of *The Journal of Physiology*, Mihara *et al.* (2011) describe the expression of another important molecular sensor, TRPV4, in mouse oesophageal keratinocytes. TRPV4 is a cation-selective channel that is activated by various physical and chemical stimuli, including heat, mechano-stimuli, endogenous substances such as arachidonic acid and its metabolites (epoxyeicosatrienoic acids), endocannabinoids and synthetic α-phorbol derivatives. This ion channel is highly expressed in skin keratinocytes and epithelia lining tubular structures throughout the body. As such, this ion channel functions as a polymodal cellular sensor and is involved in many different cellular functions, including ciliary transport in the Fallopian tubes, mechano-sensation in the urinary bladder and epidermal permeability control (Everaerts *et al.* 2010).

Mihara *et al.* describe the expression of TRPV4 mRNA and protein in mouse oesophageal epithelium and cultured oesophageal keratinocytes. In these cultured cells they demonstrate TRPV4-like currents in response to the TRPV4-selective agonists 4α-phorbol didecanoate (4α-PDD) and GSK1016790A, moderate heat and cellular stretch. These stimuli also induced TRPV4-mediated elevations of intracellular Ca^{2+}. Importantly, the authors establish a contribution of TRPV4 to heat and stretch-evoked ATP release by oesophagal epithelial cells (Mihara *et al.* 2011).

ATP is considered an important neurotransmitter in the oesophagus, since a large proportion of spinal and vagal afferents responds to ATP. Purinergic (P2X) receptor immunoreactivity has been shown in intraganglionic laminar endings, specialized vagal nerve endings involved in mechano-sensation, and in sensory nerve fibres in close proximity to the epithelium, enabling crosstalk between epithelium and sensory afferents. The functional importance of this purinergic signalling pathway was confirmed by showing blunted neuronal responses to oesophagal distension in mice lacking functional $P2X_3$ receptors (McIlwrath *et al.* 2009).

Thus, in response to oesophagal distension, TRPV4 induces Ca^{2+} influx in oesophagal keratinocytes, with subsequent ATP release, activation of neuronal P2X receptors and depolarization of afferent nerve fibres. This mechanism of neuronal–epithelial crosstalk is very similar to the proposed mechanism of TRPV4-mediated mechano-sensation by urothelial cells in the bladder (Everaerts *et al.* 2010). Importantly, this mechanism can be sensitized during cystitis, leading to functional bladder disorders. Whether a similar sensitization occurs in patients with reflux oesophagitis remains elusive, but it has already been reported that P2X receptor expression in oesophagal afferents is upregulated during inflammation.

Although the concept of epithelial ATP release is generally accepted, the cellular pathway for releasing ATP remains controversial. Mihara *et al.* suggest that Ca^{2+}-induced exocytosis is the main pathway for ATP release by oesophagal keratinocytes (Mihara *et al.* 2011). However, in a recent report, Ueda *et al.* (2011) excluded a contribution of exocytosis and propose connexin hemichannels to release ATP from oesophagal keratinocytes. Moreover, ATP is clearly not the only signalling molecule in neuronal–epithelial crosstalk. More research is needed to determine the nature of epithelial signal transmitters and to determine the relative contribution of ATP.

Recently, the presence of TRPV4 has also been demonstrated in keratinocytes of the human oesophagus, confirming interspecies conservation of TRPV4 expression (Ueda *et al.* 2011). In these cells, agonist-induced activation of TRPV4 not only stimulated ATP release, but also influenced keratinocyte proliferation. This suggests that, similar to dermal keratinocytes, TRPV4-mediated processes may not only contribute to mechano-sensation, but also influence epithelial permeability and cellular proliferation. In patients with GERD, disruption of the tight mucosal barrier is

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considered one of the critical events in the pathogenesis of acid-induced heartburn symptoms.

The characterization of TRPV4 as a potential heat- and mechano-sensor in the oesophageal epithelium significantly advances our insights about the sensory properties of these cells. Nevertheless, the functional role of TRPV4 in oesophageal physiology and especially in GERD remains elusive. Fortunately, the availability of TRPV4 knock-out mice and the recent development of TRPV4-selective antagonists, such as HC-067047, offer new opportunities to determine the (patho)physiological role of oesophageal TRPV4 *in vivo*.

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