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Epithelial acetylcholine – a new paradigm for cholinergic regulation of intestinal fluid and electrolyte transport

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A primary function of the colonic epithelium is to transport fluid and electrolytes to and from the lumen. Absorption, driven by cation absorption, is necessary for conservation of the large volumes of water that enter the intestine each day. On the other hand secretion, driven by Cl⁻ secretion, is important for hydration of the mucosal surface and maintenance of barrier function. The balance between absorptive and secretory processes is dynamic and can rapidly change either in response to normal physiological stimuli or as a consequence of disease. Central to the regulation of intestinal water transport is acetylcholine (ACh), the predominant neurotransmitter of the enteric nervous system. Cholinergic secretomotor neurons are found in close apposition to the epithelium throughout the intestine and when activated they release of ACh into the neuroepithelial junction to stimulate secretion from the crypts and inhibit absorption across the surface cells.

In this issue of the *Journal of Physiology*, Yajima and co-workers publish data which changes the way we see ACh as a regulator of intestinal secretory function. Using voltage-clamped sections of rat colon, they show that upon luminal stimulation with a short chain fatty acid (SCFA), propionate, ACh is released on the basolateral side, whereupon it interacts with muscarinic receptors to mediate secretory responses. This response occurs independently of neuronal involvement. Importantly, they also show that the molecular elements necessary for the synthesis of ACh, namely choline acetyltransferase (ChAT) and OCT transporters for the uptake of choline, are present in colonic epithelial cells. Based on their data, ACh release from the colonic epithelium fulfils many of the criteria to be considered as part of the non-neuronal cholinergic system (Shah *et al.*, 2009).

While the findings of Yajima and co-workers are of great importance for our understanding of mechanisms that regulate intestinal transport, the idea that ACh can act as an intercellular messenger, independently of its role as a neurotransmitter, is not new. In fact, non-neuronal cells, including those of the heart, lungs, vasculature, immune cells, bone and brain have been known for many years to have the capability to synthesise and release ACh. In the intestine non-neuronal ACh release was identified more than a decade ago (Klapproth *et al.*, 1997), although its physiological relevance is still poorly defined. While the current findings of Yajima and co-workers provide valuable insights, like all good research, their study raises many more questions than it provides answers. Not least among these is the physiological relevance of ACh-induced secretion in response to SCFAs. When considering this, the ACh-mediated prosecretory actions of SCFAs reported here must be reconciled with their long-established anti-secretory and proabsorptive actions. When such complex actions are considered together, one can envisage SCFA-induced ACh release as part of a localised, and well-coordinated, response to the passage of food through the intestine. Thus, as a fibrous food bolus moves through the colonic lumen and SCFAs are released due to bacterial metabolism, a rapid non-neuronal ACh-mediated secretory response occurs. Presumably, such prosecretory effects would serve to augment those mediated by neuronal

reflex arcs which are also believed to be important in lubricating the mucosa. However, these prosecretory responses are rapid and short lived and after the food bolus has passed, one might expect that direct actions of SCFAs on the epithelium would dampen secretion from the crypts and promote absorption across the surface cells (Binder, ; Krishnan *et al.*, 1999). Then, in the more long-term, ACh release, either from nerves or the epithelium, could bring about a proliferative response that may serve to replenish lost epithelial cells sloughed off during passage of the food bolus. In this way, epithelial ACh release in response to SCFAs could play an important physiological role in protecting against losses in barrier function during digestion.

To appreciate the findings of Yajima *et al* more fully, it is also important to consider the potential effects of non-neuronal ACh on other aspects of intestinal mucosal physiology. At the level of the epithelium ACh not only regulates ion transport but also proliferation, mucus secretion, cytokine production and migration. On a broader scale ACh regulates gut motility, splanchnic blood flow, and immune cell activation within the lamina propria. This situation becomes even more complex when one considers that it is not only the epithelium that can produce ACh but other cells, such as immune cells and fibroblasts, also have this capability. Thus, ACh should no longer be considered simply as a neurotransmitter but rather as a ubiquitous intercellular messenger that is likely to be important in integrating many different aspects of intestinal physiology in health and disease. Indeed, the cholinergic nervous system is often referred to as the “cholinergic anti-inflammatory system” since ACh has been shown to be protective in animal models of inflammatory bowel disease and to prevent carcinogenesis (Tracey, 2007). Interestingly, SCFAs have similar beneficial effects and the question arises as to precisely how much of a role non-neuronal ACh plays in mediating these actions.

The work presented by Yajima and co-workers in this issue of the *Journal of Physiology* is an important step forward in our understanding of intestinal physiology but there is clearly much to be learned. At the extracellular level we need to determine what other luminal factors are involved in regulating ACh release from the epithelium, while at the molecular level developing our understanding of factors that control the expression ChAT and mechanisms that govern the release of ACh from epithelial cells is of paramount importance.

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