Unravelling the secrets of the caecum

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Localized at the critical junction between the non-fermentative and fermentative parts of the gut, the caecum has a plethora of poorly understood functions. In herbivorous species, the caecum forms a large, blind pouch in which otherwise indigestible fibres are broken down into energy-rich compounds required for survival (Fig. 1). Conversely, the human caecum and its appendix are generally considered to be vestigial “troublemakers” that require removal in diseases such as inflammatory bowel disease or cancer. Recently, a role in regulating the microbiome in health and disease is being discussed [11] and a better understanding of the organ appears overdue.

As digesta enters from the ileum into the caecum, bacterial counts surge to levels above 10^{11} CFU/mL. The first function of the caecum is clearly to ensure that this dramatic switch occurs in a manner that does not endanger either the epithelium per se or the microbes within. To maintain fermentational homeostasis, microbial products such as short chain fatty acids or ammonia must be absorbed to prevent an accumulation to toxic levels, and buffers must be secreted to maintain an optimal pH [3]. Equally important, the caecal epithelium must form a tight mechanical and immunological barrier against an efflux of microbes and their toxins into the bloodstream.

The combination of epithelial tightness and high levels of transport invite electrophysiological investigations which yield insights not only concerning the caecal epithelium, but possibly enhancing our understanding of the function and regulation of the underlying transport

proteins within an intact epithelium. Building on two previous studies published in *Pflügers Arch.* [1, 2], in the current issue, Pouokam and Diener systematically compare differences in ion transport across two different segments of the rat caecum [8]. As in the classical model, a basolateral NKCC drives secretion via anion channels, possibly delivering HCO_3^- to deliver protons formed in the fermentational process [6, 10]. However, amiloride in the micromolar quantities normally known to block ENaC failed to show effects. This finding is in line with previous observations in the proximal rat colon [5] and rabbit caecum [4], with the latter expressing an apical cation conductance permeable to cations as diverse as Na^+ , K^+ , Cs^+ or Rb^+ [13]. Pouokam and Diener now take the story one step further by showing that in rat, this non-selective cation conductance is sensitive to TRP channel modulators. In a further twist, they demonstrate that both the anionic and the cationic conductances are significantly upregulated by cyclooxygenase metabolites—with signalling strongest in the distal caecum, where metabolites tend to accumulate.

Given the classical observation that the apical membrane of the caecum is poorly permeable to NH_3 [3] and that TRP channels are notoriously promiscuous [7], TRP channels may provide a venue for the efflux of NH_4^+ from the caecum, as suggested for the rumen [9, 12]. Regulation of bicarbonate influx and ammonia efflux by neural and paracrine signalling would certainly enhance the ability of the caecum to regulate caecal pH and nitrogen levels as key factors in maintaining a healthy microbial equilibrium.

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Fig. 1 The primordial function of the caecum is to serve as a fermentation chamber in which otherwise indigestible carbohydrates are fermented by a resident microbial population (①) to release metabolites such as short chain fatty acids (SCFA, ②) that are utilized to meet the energy demands of the host (③). In the process, protons and ammonia are produced and must be kept at optimal levels via buffering (④), microbial protein

synthesis or efflux (⑤). Paracrine and neuronal signalling via eicosanoids and acetylcholine is highest in the aboral parts of the caecum and stimulates anion (⑥) and cation channels (⑦). It is tempting to speculate that the non-selective nature of these conductances plays a role in maintaining fermentational equilibrium.

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