ClC-2 and intestinal chloride secretion

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TO THE EDITOR: Beyder and Farrugia (1) state in their recently published review that lubiprostone is an opener of ClC-2 chloride channels and that through that action it can ameliorate constipation, implying that ClC-2 would mediate chloride and therefore fluid secretion. Support for this claim is provided through citation of a previous review (8). Nevertheless, both reviews overlook evidence clearly rebutting such view. This evidence is briefly summarized below:

1) The evidence for ClC-2-mediated chloride secretion relies on the apparent expression of ClC-2 at the apical membrane of epithelial cell lines. However, immunolocalization studies in human, mouse, guinea pig, and rat intestine have clearly demonstrated that ClC-2 is preferentially located basolaterally (3, 5-7). Even though in one of these publications ClC-2 was observed at the apical membrane of surface epithelial cells, their function as a bona fide chloride secretion channel is questioned owing to its very low expression at the upper reaches of the crypts, where chloride secretion is not likely to occur due the absence of NKCC1 and of basolateral potassium channels (KCNQ1/KCNE3 and KCNN4) necessary for sustained chloride secretion (6).

2) ClC-2 silencing in mouse intestine does not produce a CF-like phenotype as would be expected from apical membrane localization. Instead, it was shown that ClC-2 absence increases the chance of survival of the Cfr<sup>−/−</sup> mice, that are severely affected by intestinal obstructions (9).

3) In accordance with the immunolocalization data, it was suggested that ClC-2 must be involved in electroneutral absorption of NaCl. The functional evidence was provided when a significant reduction of chloride absorptive flux was reported in the colon from ClC-2 null mice (4). Such observation can explain the improved survival of the CF mice when ClC-2 gene expression is additionally silenced (9).

4) Finally, lubiprostone fails to induce chloride secretion in human and mouse colon when CFTR was not present (2), suggesting that it is this protein that is targeted by the drug in the intestinal epithelium.

Taken together, the evidence compiled here argues against a role for ClC-2 in intestinal chloride secretion and therefore makes it unlikely that the effect of lubiprostone is exerted by an action as an opener of ClC-2 channels. We believe that all this information must be considered when the function of ClC-2 in intestinal epithelium is being discussed.

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REFERENCES