Critical Reviews in Biochemistry and Molecular Biology, 2009; 44(4): 243–244

informa
healthcare

Erratum

The publisher would like to apologise for a typesetting error in Letters to the Editor, Critical Reviews in Biochemistry and Molecular Biology 2009; 44(2–3):63–4. In the exchange of correspondence between Dr. Ueno and Professor Jentsch, the authors' names were inverted in error. As a courtesy to the authors and our readers, we are republishing the correspondence on page 243–244 following.

The full citation is:

Ueno R; Jentsch TJ. Comment and reply on: CLC chloride channels and transporters: from genes to protein structure, pathology and physiology. Crit Rev Biochem Mol Biol 2009; 44(4): 63 and 64.

TO THE EDITOR

Comment and reply on: CLC chloride channels and transporters: from genes to protein structure, pathology and physiology

Ryuji Ueno, M.D., Ph.D., Ph.D.

Chairman and Chief Executive Officer of Sucampo Pharmaceuticals, Inc.
Sucampo Pharmaceuticals 4520 East-West Highway, 3rd Floor Bethesda, MD 20814

The recent article by Jentsch TJ (1) reports that, "the contention that lubiprostone activates ClC-2 [type 2 chloride channels] is questionable …" Furthermore, it states that, "ClC-2 activation might rather be useful in diarrhea, but detrimental in obstipation."

Subsequent to this review article, studies were published using HEK293 cells transfected with human ClC-2 in single channels. The results from these trials confirm that lubiprostone activates ClC-2 (2).

Lubiprostone is a prostone that has been extensively shown to treat constipation in well-controlled clinical trials involving thousands of humans (3,4). Lubiprostone received approval from the United States Food and Drug Administration in 2006 under the trade name AMITIZA® for the long-term treatment of chronic idiopathic constipation in adults (5). The approved labeling specifically includes a contraindication to lubiprostone's use in severe diarrhea.

The inference that lubiprostone might be useful in the treatment of diarrhea and contraindicated with constipation is medically unsound.

References

1. Jentsch TJ. 2008. CLC chloride channels and transporters: from genes to protein structure, pathology and physiology. *Crit Rev Biochem Mol Biol*. 43:3–36.
2. Bao HF, Liu L, Self J, Duke BJ, Ueno R, and Eaton D. 2007. A synthetic prostone activates apical chloride channels in A6 epithelial cells. 2008. *Am J Physiol Gastrointest Liver Physiol*. 295:234–251.
3. Johanson JF and Ueno R. 2007. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther*. 25:1351–1361.

ISSN 1040-9238 print/ISSN 1549-7798 online © 2009 Informa UK Ltd
DOI: 10.1080/10409230903195666

4. Johanson JF, Morton D, Geenen J, and Ueno R. 2008. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol*. 103(1):170–177.
5. Amitiza [package insert]. 2008. Bethesda, MD: Sucampo Pharmaceuticals, Inc.

Author's Reply

Dr. Thomas J. Jentsch, Professor

Leibniz-Institut für Molekulare Pharmakologie (FMP) and Max-Delbrück-Centrum für Molekulare Medizin (MDC), Robert-Rössle-Strasse 10, Haus 87, D-13125 Berlin, Germany

In his letter, Dr. Ueno of Sucampo Pharmaceuticals writes that my review article (1) suggests that lubiprostone is useful to treat diarrhea and is contraindicated in obstipation. This is not true. I made no statement as to the clinical effects of lubiprostone. I raised, however, well-founded doubts about the contention that lubiprostone activates ClC-2. Indeed, the only paper available that supported such a role of lubiprostone at the time of publication of my review showed effects of lubiprostone on currents that displayed a linear I/V relationship (2). These currents are very unlikely to represent ClC-2, which rather mediates inwardly rectifying currents that are slowly activated by hyperpolarization (as published by at least five independent laboratories including my own). Unfortunately, Dr. Ueno, Sucampo, as well as all authors publishing on lubiprostone that I contacted, refused to provide that substance for studying its effect on ClC-2. Therefore, independent tests of lubiprostone on ClC-2 currents have not been possible.

The only knock-out controlled immunohistochemical analysis of ClC-2 available (3,4; and own unpublished results) shows that ClC-2 can be detected in basolateral, but not in apical membranes of intestinal epithelial cells. A basolateral localization of ClC-2 is also compatible with Ussing chamber experiments performed on WT and ClC-2 KO colon (5). As stated in my review, a basolateral localization of ClC-2 suggests that its activation should increase chloride and water reabsorption. Hence, *if* lubiprostone would exert its intestinal effects through an activation of ClC-2, it should worsen rather than alleviate obstipation – an effect which is obviously in contrast to several published reports. In summary, I question the contention that lubiprostone ameliorates obstipation by activating ClC-2.

References

1. Jentsch T.J. (2008). CLC chloride channels and transporters: From genes to protein structure, pathology and physiology. *Crit. Rev. Biochem. Molec. Biol.* 43, 3–36.
2. Cuppoletti J, Malinowska DH, Tewari KP, Li QJ, Sherry AM, Patchen ML, Ueno R. (2004) SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. *Am J Physiol Cell Physiol*. 287, C1173–C1183.
3. Peña-Münzenmayer G, Catalán M, Cornejo I, Figueroa CD, Melvin JE, Niemeyer MI, Cid LP, Sepúlveda FV. (2005) Basolateral localization of native ClC-2 chloride channels in absorptive intestinal epithelial cells and basolateral sorting encoded by a CBS-2 domain di-leucine motif. *J Cell Sci.*118, 4243–4252.
4. Catalán M, Cornejo I, Figueroa CD, Niemeyer MI, Sepúlveda FV, Cid LP. (2002) ClC-2 in guinea pig colon: mRNA, immunolabeling, and functional evidence for surface epithelium localization. *Am J Physiol Gastrointest Liver Physiol*. 283, G1004–G1013.
5. Zdebik A.A., Cuffe J., Bertog M., Korbmacher C., Jentsch T.J. (2004). Additional disruption of the ClC-2 Cl^- channel does not exacerbate the cystic fibrosis phenotype of CFTR mouse models. *J. Biol. Chem.* 279, 22276–22283.