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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Dynamics of Intestinal Calcium Absorption in Neonates

Calcium surveillance from the intestinal lumen is critical for growth and maintaining homeostasis. Different regions of the intestine employ distinct mechanisms of calcium absorption, including paracellular and transcellular pathways through diverse transporters. This segmental heterogeneity is likely a reflection of luminal calcium forms and concentrations, although bioavailability of dietary calcium and its interaction with macronutrients are not fully understood. Gastric acid is necessary to solubilize Ca^{2+}, and rats that underwent Roux-en-Y reconstruction with total gastrectomy showed impaired bone mineralization with an approximately 80% decrease in apparent calcium absorption.[1] This suggests that both gastric acid and the duodenum play large roles in dietary calcium absorption. Indeed, the predominant expression of transcellular calcium transporters was localized to the duodenum of adult mice and humans.[2] Transcellular Ca^{2+} absorption is adenosine triphosphate dependent and mediated by the apical membrane calcium channel TRPV6 (also known as CaT1 or ECaC2), basolateral sodium-calcium exchanger (NCX) 1, the plasma membrane calcium pump (PMCA) 1b, and the intracellular calcium binding protein S100-G (calbindin-D_{9k}, known as CaBP). Transcription of *Trpv6* and *S100g* is increased by the vitamin D metabolite 1,25-$[OH]_2D_3$, indicating hypocalcemia, and is suppressed by the extracellular Ca^{2+} receptor (CaSR) activation, indicative of hypercalcemia in the duodenum and proximal colon of mice.[2,3] Jejunal calcium absorption has been found through apical L-type Ca^{2+} channel(s), such as $Ca_{v1.3}$, and is enhanced by high concentrations of glucose in rats.[4] Dietary factors are known to influence calcium absorption (eg, casein and lactose enhance, but phytic acid and oxalic acid inhibit absorption). While milk is commonly believed to be the best source of calcium, the molecular mechanisms by which organic compounds in milk facilitate calcium absorption need to be confirmed.

Until recently, little was known on the mechanisms of Ca^{2+} absorption in the developing neonate. A study presented by Beggs et al[5] in the current issue of *Cellular and Molecular Gastroenterology and Hepatology* thoroughly investigated the developmental changes in the functional expression of Ca^{2+} transporters among the small intestine in mice. The expression of calbindin-D_{9k} appeared after weaning in the duodenum, whereas the jejunum and ileum demonstrated a reciprocal pattern, indicating a dynamic change in the transcellular Ca^{2+} absorption site. Using mice with germline mutations in *Trpv6* or *Cacna1d* ($Ca_{v1.3}$), their work highlighted the importance of these channels in Ca^{2+} absorption in the distal small intestines of preweaned mice, rather than in the duodenum. $Ca_{v1.3}$ deficiency delayed mineral accumulation in the trabecular bone, suggesting that $Ca_{v1.3}$ plays a crucial role in bulk Ca^{2+} uptake. Further early weaning experiments demonstrated that the termination of milk feeding differently altered the expression of those Ca^{2+} transporters in the distal small intestine. Their novel findings, which disclosed that the developing distal small intestine actively absorbs Ca^{2+} until weaning in mice, suggest the dynamics in developmental and adaptative gastrointestinal physiology also in humans.

While molecular techniques such as in situ hybridization and immunohistochemistry have aided in the identification of nutrient transporters and their segmental heterogeneity, the Alexander group[3,5] has employed the Ussing chamber system (ex vivo). This classic electrophysiological assay is suited to quantifying transporter functions, especially in the transcellular pathway under voltage-clamping (short-circuit) conditions and is able to simultaneously compare diverse regions. A gas-lift chamber comprised of twin compartments separately bathing the luminal and serosal surfaces, similar to in situ conditions, allows the testing of whether luminal buffer composition or osmolarity affects molecular transport activities across the mucosa. As luminal flow is likely essential for epithelial viability, this gas-lift system works well for investigating physiological transporter functions in tissues and cultured polarized cells, rather than in transwells or tissue incubation in the plates. In fact, recent developments in monolayered enteroids from human specimens and genetically modified animals are applicable to the Ussing chamber system and are expected to reveal more precise molecular mechanisms and cellular interactions of epithelial transport functions.

The present report demonstrates the importance of $Ca_{v1.3}$ in the intestinal Ca^{2+} uptake and its resulting bone accumulation early in life and shows that preweaned mice have a different strategy for calcium absorption than adults. Their results will no doubt spur further research into the absorption mechanisms of other essential trace elements, which are required for infant development.

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Conflicts of interest
The author discloses no conflicts.


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2352-345X
https://doi.org/10.1016/j.jcmgh.2019.08.010