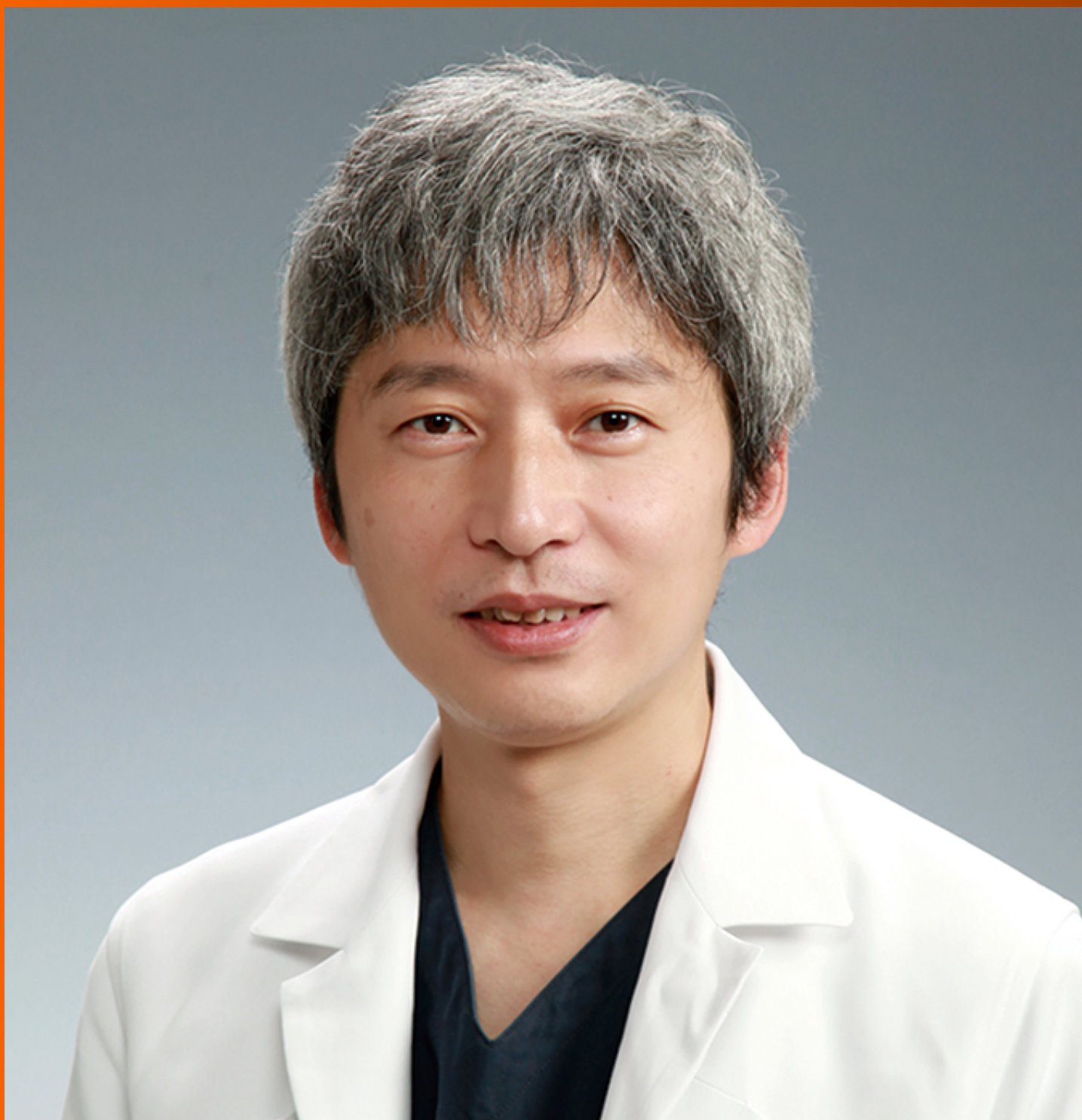


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## Current opinion on the regulation of small intestinal magnesium absorption

Siriporn Chamniansawat, Nasisorn Suksridechacin, Narongrit Thongon

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### Abstract

Magnesium ( $Mg^{2+}$ ) has an important role in numerous biological functions, and  $Mg^{2+}$  deficiency is associated with several diseases. Therefore, adequate intestinal absorption of  $Mg^{2+}$  is vital for health. The small intestine was previously thought to absorb digested  $Mg^{2+}$  exclusively through an unregulated paracellular mechanism, which is responsible for approximately 90% of total  $Mg^{2+}$  absorption. Recent studies, however, have revealed that the duodenum, jejunum, and ileum absorb  $Mg^{2+}$  through both transcellular and paracellular routes. Several regulatory factors of small intestinal  $Mg^{2+}$  uptake also have been explored, *e.g.*, parathyroid hormone, fibroblast growth factor-23, apical acidity, proton pump inhibitor, and pH-sensing channel and receptors. The mechanistic factors underlying proton pump inhibitor suppression of small intestinal  $Mg^{2+}$ , such as magnesiotropic protein dysfunction, higher mucosal bicarbonate secretion, Paneth cell dysfunction, and intestinal inflammation, are currently being explored. The potential role of small intestinal microbiomes in  $Mg^{2+}$  absorption has also been proposed. In this article, we reviewed the current knowledge on the mechanisms and regulatory factors of small intestinal  $Mg^{2+}$  absorption.

**Key Words:** Hormone; Magnesium absorption; Paneth cells; Proton pump inhibitor; Regulation; Small intestine

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**Core Tip:** Small intestinal epithelium absorbs digested magnesium ( $Mg^{2+}$ ) through both transcellular active and paracellular passive mechanisms. Several regulatory factors of small intestinal  $Mg^{2+}$  uptake have been reported. Parathyroid hormone and fibroblast growth factor-23 directly inhibit transcellular  $Mg^{2+}$  absorption in the duodenum, jejunum, and ileum. The apical proton triggers acid-sensing ion-channel 1a and purinergic  $P2Y_2$  receptor activities, which stimulates mucosal bicarbonate secretion and induces  $MgCO_3$  precipitation to suppress absorption. Omeprazole suppresses  $Mg^{2+}$  absorption in the duodenum, jejunum, and ileum.

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## INTRODUCTION

Magnesium ( $Mg^{2+}$ ) has an essential role in numerous cellular biochemical functions ranging from DNA structure stability and repairing, cell proliferation, neuronal excitability, bronchodilatation, vasodilatation, muscle contraction, myocardial excitability, bone hydroxyapatite formation, and anti-inflammatory function to exocrine and endocrine function of the pancreas[1].  $Mg^{2+}$  deficiency has been implicated in several diseases, such as Alzheimer's disease[2], osteoporosis[3], hypertension[4], diabetes mellitus[5], and cancer[6]. Therefore, its plasma level is tightly regulated within a narrow range (0.7-1.1 mmol/L) by the collaborative actions of intestinally digested  $Mg^{2+}$  absorption, bone and muscle  $Mg^{2+}$  storage, and excess renal  $Mg^{2+}$  excretion[1]. The mechanism underlying regulation of transepithelial  $Mg^{2+}$  transport has been extensively explored in the renal tubular epithelium[1]. However, few research articles on the mechanism and regulatory factors of intestinal  $Mg^{2+}$  absorption have been published.

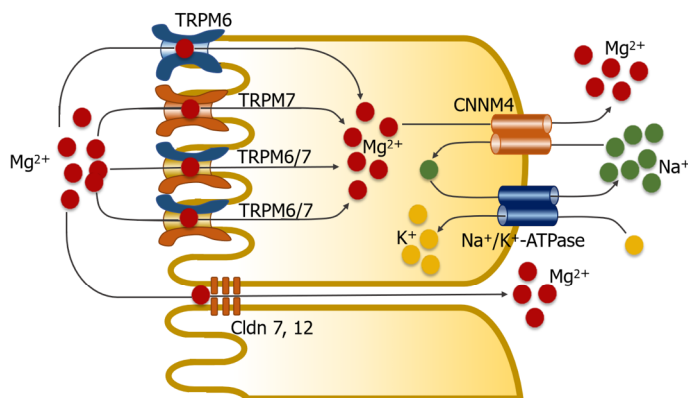
Since dietary intake is the sole source of  $Mg^{2+}$  in humans, adequate intestinal absorption of  $Mg^{2+}$  is vital for normal  $Mg^{2+}$  balance. It was previously hypothesized that bulk  $Mg^{2+}$  uptake occurs in the small intestine through an unregulated paracellular pathway, whereas fine-tuning of colonic  $Mg^{2+}$  absorption occurs through a regulated transcellular mechanism[1,7,8]. Colonic  $Mg^{2+}$  absorption can be modulated by dietary  $Mg^{2+}$  content and inulin fibers[7,9] but not by hormones[1,7]. In contrast, recent studies have provided new insights into the mechanisms and modulatory factors of small intestinal  $Mg^{2+}$  uptake. The aim of this article was to review the current knowledge of the mechanisms and regulatory factors of small intestinal  $Mg^{2+}$  absorption.

## MECHANISM OF SMALL INTESTINAL $Mg^{2+}$ ABSORPTION

The mechanism of small intestinal  $Mg^{2+}$  absorption is currently under debate. One research group has proposed that transient receptor potential melastatin 6 homodimer channel (TRPM6) mRNA expression and transcellular  $Mg^{2+}$  absorption were not present in the small intestine[1,7,8]. However, a study from the same group showed positive immunofluorescence staining of TRPM6 protein in the absorptive cells along the brush border membrane of the villi in the duodenum[10]. Another group has proposed that the small intestinal epithelium absorbs  $Mg^{2+}$  through transcellular active and paracellular passive transport mechanisms[11-13]. In an Ussing chamber study, transport of transcellular and paracellular  $Mg^{2+}$  was detected in the duodenum, jejunum, and ileum[11-13]. The proposed mechanism of small intestinal  $Mg^{2+}$  absorption is shown in Figure 1.

### Transcellular $Mg^{2+}$ absorption

Transcellular  $Mg^{2+}$  absorption occurs through mucosal  $Mg^{2+}$  uptake by TRPM6 and TRPM7 homodimer channel, both of which were markedly detected in the small intestinal epithelium of human and murine cells[10-14]. In addition, recent mass spectrometric peptide sequence analysis confirmed the expression of TRPM6 and TRPM7 in the duodenum and jejunum[15]. The channel activities of both homodimers of TRPM6 and of TRPM7 are negatively regulated by physiological  $Mg \cdot ATP$  and  $Mg^{2+}$  levels[10,16-19]. A recent study reported the expression of a heterodimer TRPM6/7 channel in the plasma membrane of duodenal and jejunal epithelium[15]; therefore,  $Mg^{2+}$  enters the small intestinal epithelial cells through TRPM6/7, TRPM6, and TRPM7. However, the heterodimer TRPM6/7 channels do not respond to physiological intracellular  $Mg^{2+}$  and  $Mg \cdot ATP$ [17,19]; thus, continuous epithelial  $Mg^{2+}$  absorption can occur through the TRPM6/7 channel, regardless of intracellular  $Mg^{2+}$  and concentrations. Basolateral  $Mg^{2+}$  extrusion from the small intestinal epithelium occurs through cystathionine  $\beta$ -synthase domain divalent metal cation transport mediator 4[11-13,20] by means of a sodium ( $Na^+$ ) gradient-dependent



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**Figure 1 Magnesium absorption in the small intestine through two absorption pathways.** The transcellular transport mechanism involves magnesium ( $Mg^{2+}$ ) influx into enterocytes through the transient receptor potential melastatin 6 homodimer channel (TRPM6), transient receptor potential melastatin 7 homodimer channel (TRPM7), and transient receptor potential melastatin 6/7 heterodimer channel (TRPM6/7). Cystathionine  $\beta$ -synthase domain divalent metal cation transport mediator 4 (CNNM4) mediates basolateral  $Mg^{2+}$  extrusion by means of secondary active transport. In the paracellular mechanism,  $Mg^{2+}$  moves through tight-associated paracellular pores of Claudin (Cldn 7) and Claudin 12 (Cldn 12).

secondary active transport[20]. However, mutation of cystathionine  $\beta$ -synthase domain divalent metal cation transport mediator 4 does not affect the plasma concentration in humans[21,22], suggesting that other  $Mg^{2+}$  extrusion mechanisms probably occur.

#### Paracellular $Mg^{2+}$ absorption

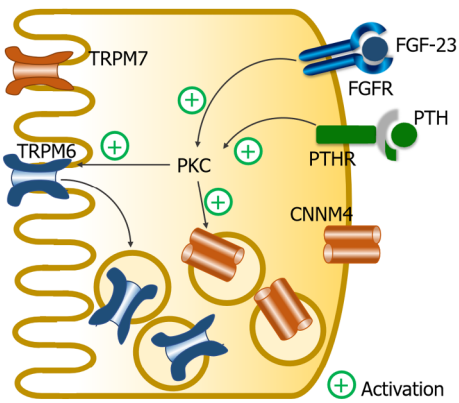
It has been suggested that paracellular  $Mg^{2+}$  absorption is responsible for 90% of total intestinal  $Mg^{2+}$  uptake[23]. Paracellular permeability is regulated by the paracellular claudin (Cldn) channel of the tight junction[24]. In 1999, the first discovery of a paracellular channel at the tight junction was Cldn-19 or paracellin-1, which form a paracellular  $Mg^{2+}$  channel[25]. It is thought that paracellular  $Mg^{2+}$  channels in epithelial tissues are formed by Cldn-16 and -19[25-27]; mutations in these genes lead to severe hypomagnesemia. The small intestinal epithelium expresses Cldn-1-5, -7, -8, -12, and -15 but not -16 and -19[28,29]. A previous study proposed that Cldn-7 and -12 modulated intestinal paracellular  $Mg^{2+}$  absorption[30]. However, the processes involving Cldn-regulated paracellular  $Mg^{2+}$  absorption in the small intestine still must be elucidated.

## REGULATORY FACTORS OF SMALL INTESTINAL $Mg^{2+}$ ABSORPTION

### Hormones

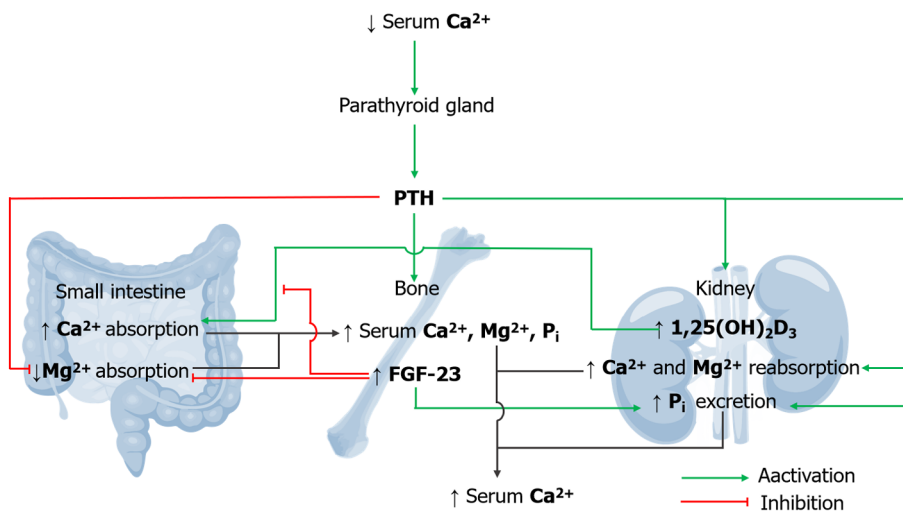
In general, hormones mainly modulate the transcellular electrolyte transport to regulate epithelial electrolyte absorption or secretion. Hormonal regulation of small intestinal  $Mg^{2+}$  absorption also modulates transcellular  $Mg^{2+}$  absorption. A recent study reported that parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) systemically and directly inhibited transcellular, but not paracellular,  $Mg^{2+}$  absorption in the duodenum, jejunum, and ileum[13]. There was no additional effect of PTH and FGF-23, suggesting that they acted through the same intracellular signaling molecule. Both PTH and FGF-23 activate their corresponding receptors that further stimulate the same protein kinase C pathway to suppress plasma membrane-associated TRPM6 expression (Figure 2). Since native TRPM6 primarily functions as a subunit of heteromeric TRPM6/7 channels[31], the suppression of plasma membrane TRPM6 probably suppresses plasma TRPM6/7 heterodimer expression. The suppression of plasma TRPM6 and TRPM6/7 activity leads to diminution of transcellular  $Mg^{2+}$  absorption[13]. The inhibitory effect of PTH and FGF-23 could be nullified by Gö 6850[13], which inhibits the conventional ( $\alpha$ ,  $\beta$ 1,  $\beta$ 2, and  $\gamma$ ) and novel ( $\delta$  and  $\epsilon$ ) protein kinase C isoforms. However, the exact signaling pathway of PTH and FGF-23 inhibition of small intestinal transcellular  $Mg^{2+}$  absorption requires further study.

The proposed physiologically relevant magnesiotropic actions of PTH and FGF-23 are shown in Figure 3. During hypocalcemia, the parathyroid gland actively secretes PTH into the blood stream. PTH stimulates the bone resorption process, which increases plasma calcium ( $Ca^{2+}$ ), inorganic phosphate (Pi), and  $Mg^{2+}$  levels[32,33]. PTH stimulates renal 1,25-dihydroxy vitamin  $D_3$  [ $1,25(OH)_2D_3$ ] production, which subsequently induces small intestinal  $Ca^{2+}$  absorption[34]. PTH also activates renal tubular  $Ca^{2+}$  and  $Mg^{2+}$  reabsorption[32]. Plasma Pi and PTH trigger bone-derived FGF-23 release, which acts as a negative feedback regulator to abolish  $1,25(OH)_2D_3$ -induced intestinal  $Ca^{2+}$  absorption[33]. PTH and FGF-23 synergistically suppress the small intestinal absorption of dietary  $Mg^{2+}$ [13] to prevent hypermagnesemia. PTH and FGF-23 downregulate the  $Na^+$ -dependent Pi cotransporters, (NaPi)-IIa and NaPi-IIc,



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**Figure 2 Fibroblast growth factor-23 and parathyroid hormone regulate magnesium absorption in the small intestine.** Fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH) act through their corresponding receptors to suppress magnesium absorption in the protein kinase C (PKC)-dependent pathway; they suppressed membrane transient receptor potential melastatin 6 homodimer channel (TRPM6) expression, which leads to the suppression of membrane transient receptor potential melastatin 6/7 (TRPM6/7) expression. FGF-23 and PTH also increase cytosolic cystathionine  $\beta$ -synthase domain divalent metal cation transport mediator 4 (CNNM4) expression. TRPM7: Transient receptor potential melastatin 7 homodimer channel; FGFR: Fibroblast growth factor receptor; PTHR: Parathyroid hormone receptor.



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**Figure 3 Integrated magnesiotropic action of fibroblast growth factor-23 and parathyroid hormone.** Parathyroid hormone (PTH) stimulates the bone resorption process, which increases plasma calcium ( $\text{Ca}^{2+}$ ), inorganic phosphate ( $\text{P}_i$ ), and magnesium ( $\text{Mg}^{2+}$ ) levels. PTH stimulates the release of 1,25-dihydroxy vitamin  $\text{D}_3$  ( $1,25(\text{OH})_2\text{D}_3$ ) to subsequently induce small-intestinal  $\text{Ca}^{2+}$  absorption. PTH also activates renal tubular  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  reabsorption. Plasma  $\text{P}_i$  and PTH trigger the release of fibroblast growth factor-23 (FGF-23) to abolish  $1,25(\text{OH})_2\text{D}_3$ -induced intestinal  $\text{Ca}^{2+}$  absorption. PTH and FGF-23 synergistically suppress small intestinal absorption of dietary  $\text{Mg}^{2+}$ . PTH and FGF-23 induce urinary  $\text{P}_i$  excretion.

and increase urinary  $\text{P}_i$  excretion[32] to prevent hyperphosphatemia. Therefore, PTH and FGF-23 exert their calcemic effect by preventing hyperphosphatemia and hypermagnesemia.

### Luminal acidity

The hypothesis that apical acidity and mucosal bicarbonate secretion (MBS) affect luminal  $\text{Mg}^{2+}$  solubility and intestinal  $\text{Mg}^{2+}$  absorption was previously proposed in 2014[11,35], which was confirmed in a recent review article[36]. The luminal acidity along the entire human and rodent small bowel varies from pH 5.0–7.3[12,37]. The luminal protons provide an appropriate environment for mineral absorption by stabilizing their ionized forms[38]. The elevation of luminal pH led to a lower soluble  $\text{Mg}^{2+}$ , which decreased from 79.61% of total luminal Mg content at pH 5.15% to 8.71% of total luminal Mg at pH 7.8[39]. Therefore, luminal acidity enhances  $\text{Mg}^{2+}$  absorption in the human small intestine[40] and epithelial-like Caco-2 monolayers[30,35]. The MBS and luminal pH elevation diminished duodenal, jejunal, and ileal  $\text{Mg}^{2+}$  absorption[11,12].



### **pH-sensing channel and receptor**

Small intestinal enterocytes are regularly exposed to strong gastric acid. When luminal protons are present in the duodenal lumen, the intestinal epithelium cells can directly detect and modulate their cellular response through the proton-sensing channels, *e.g.*, the acid-sensing ion-channel 1a (ASIC1a) or proton-sensing receptors, such as ovarian cancer G protein-coupled receptor 1 (OGR1) and P2Y<sub>2</sub> purinoceptor[41-44].

OGR1, also known as GPR68, is expressed in the human small intestine, spleen, testes, brain, lungs, placenta, heart, and kidneys but not in the colon[44]. OGR1 is a proton-sensitive receptor with pH values at half activation (pH<sub>0.5</sub>) and full activation of 7.2 and 6.8, respectively[45-47]. When the luminal pH decreases to 6.5, OGR1 activity is inactivated[45]. Activation of OGR1 triggers the phospholipase C-protein kinase C signaling pathway to activate intestinal Mg<sup>2+</sup> absorption[35] (Figure 4).

ASIC1a is a proton-sensitive Ca<sup>2+</sup> channel with a pH<sub>0.5</sub> of 6.2[41,43]. Activation of ASIC1a activates intracellular Ca<sup>2+</sup> signaling and subsequently induces MBS. In the intestinal epithelium, luminal proton stimulates ASIC1a activity that further activates MBS in a Ca<sup>2+</sup> signaling-cystic fibrosis transmembrane conductance regulator-dependent mechanism[35] (Figure 4). Secreted bicarbonate has previously been found to reduce luminal protons[48] and induce precipitation of luminal free Mg<sup>2+</sup>[49], thus reducing free soluble Mg<sup>2+</sup> and suppressing intestinal Mg<sup>2+</sup> absorption.

Purinergic regulation of luminal pH and electrolyte transport in the small intestine have been described[50-52]. Duodenocytes regularly secrete ATP into its lumen. If luminal pH is low, luminal alkaline phosphatase activity is diminished and luminal ATP increases, which subsequently activates P2Y<sub>2</sub> purinoceptor. Simultaneously, P2Y<sub>2</sub> is a proton-sensitive receptor that is activated by luminal protons[42]. Active P2Y<sub>2</sub> purinoceptors further activate MBS to increase luminal pH. A previous study showed that P2Y<sub>2</sub> activation induced MBS through a cystic fibrosis transmembrane conductance regulator- and Na<sup>+</sup>-HCO<sub>3</sub><sup>-</sup> cotransporter-1-dependent mechanism, which subsequently suppressed intestinal Mg<sup>2+</sup> absorption[53] (Figure 5).

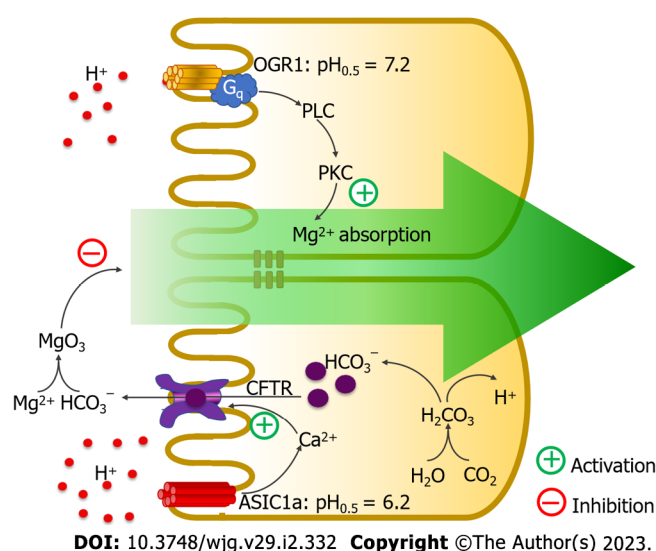
### **Proton pump inhibitor**

Proton pump inhibitor (PPI)-induced hypomagnesemia (PPIH) and hypomagnesuria in humans have been reported since 2006[54-57]. Intravenous Mg<sup>2+</sup> supplementation or withdrawal of the PPI was able to rapidly normalize plasma and urinary Mg<sup>2+</sup> levels in PPIH patients, though oral Mg<sup>2+</sup> supplementation could not. Clinical assessments have reported that PPIH patients had normal renal Mg<sup>2+</sup> handling[54,56,57]. These findings suggest that PPIs could suppress intestinal Mg<sup>2+</sup> absorption. Our group has extensively studied the underlying mechanisms of PPI-suppressed intestinal Mg<sup>2+</sup> absorption for a decade[11,12,15,30,35,53,58,59]. Our results suggest that PPIs mainly suppressed small intestinal Mg<sup>2+</sup> absorption.

Omeprazole, the first introduced PPI, significantly suppressed total, transcellular, and paracellular Mg<sup>2+</sup> absorption in the duodenum, jejunum, ileum, and colon of PPIH rats[11,12]. Regarding the percent suppression of total Mg<sup>2+</sup> absorption in the duodenum (81.86%), jejunum (70.59%), ileum (69.45%), and colon (39.25%), the small intestine is the segment most adversely affected by prolonged PPI administration. However, previous articles have proposed that PPIs mainly inhibit colonic Mg<sup>2+</sup> absorption[36,60,61], but those study results remain controversial[60,61]. They also proposed that colonic fermentation of dietary fibers probably increased serum Mg<sup>2+</sup> and cured patients with PPIH[36]. A previous study clearly showed that dietary inulin fibers significantly induced cecal and colonic fermentation, but not plasma Mg<sup>2+</sup> levels, in control and PPIH mice[61]. In contrast, dietary inulin fibers significantly induced renal Mg<sup>2+</sup> excretion in PPIH mice[61], which should aggravate hypomagnesemia in PPIH. Therefore, the large intestine may not be a suitable intestinal segment that should be modulated to counteract PPIH.

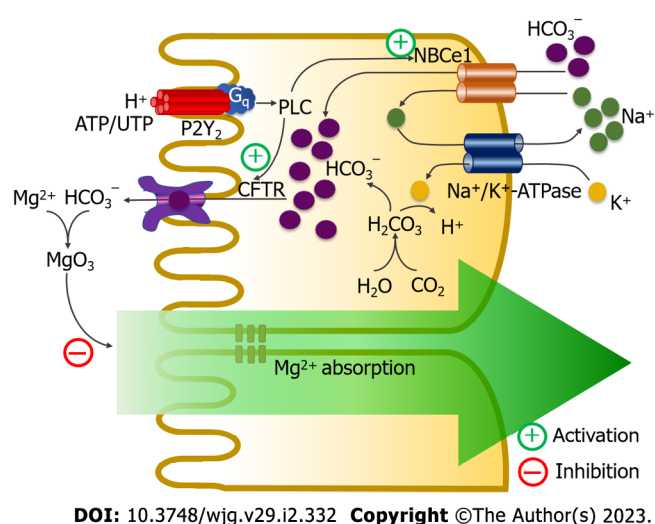
The proposed mechanism of PPI-suppression of small intestinal Mg<sup>2+</sup> absorption is shown in Figure 6. PPIs markedly suppress membranous TRPM7 and TRPM6/7[15]. Membranous TRPM6-channel activity is suppressed by hyperphosphorylation at the T1851 residue and hyperoxidation at the M1755 residue [15]. Phosphorylation of the T1851 residue of the TRPM6 protein induces TRPM6-channel suppression by intracellular free Mg<sup>2+</sup> and activated 5 C-kinase 1[62]. Oxidation of the M1755 residue in the TRPM6 protein also suppresses its channel permeability[63]. Suppression of membranous TRPM6, TRPM7, and TRPM6/7 disrupts mucosal Mg<sup>2+</sup> entry into the small intestinal epithelium and then inhibits transcellular Mg<sup>2+</sup> absorption[11,12]. Plasma FGF-23 was markedly increased in PPIH rats[12]. The mechanism by which FGF-23 inhibits transcellular small intestinal Mg<sup>2+</sup> absorption is described in the above section[13]. Therefore, PPI-suppressed transcellular Mg<sup>2+</sup> absorption is due, at least in part, to FGF-23.

PPIs suppress paracellular Mg<sup>2+</sup> absorption (Figure 6). The small intestinal epithelium only expresses Cldn-1, -2, -3, -4, -5, -7, -8, -12, and -15[28,29]. Overexpression of Cldn proteins and higher paracellular resistance have been demonstrated in the small intestines of PPIH rats[11,12]. Paracellular tight junction width was significantly decreased in the small intestine of PPIH rats[58]. PPIs also suppress epithelial paracellular Mg<sup>2+</sup> permeability and cation selectivity[30,59]. These results shed light on the mechanism of PPI-suppressed paracellular Mg<sup>2+</sup> absorption in the small intestine.



**Figure 4 Ovarian cancer G protein-coupled receptor 1 and acid-sensing ion-channel 1a modulate intestinal magnesium absorption.**

Activation of ovarian cancer G protein-coupled receptor 1 (OGR1) triggers the phospholipase C (PLC)–protein kinase C (PKC) signaling pathway to activate intestinal magnesium ( $\text{Mg}^{2+}$ ) absorption. Activation of acid-sensing ion-channel 1a (ASIC1a) activates intracellular calcium ( $\text{Ca}^{2+}$ ) signaling to induce mucosal bicarbonate secretion in a cystic fibrosis transmembrane conductance regulator (CFTR)-dependent mechanism. Secreted bicarbonate ( $\text{HCO}_3^-$ ) reduces free soluble  $\text{Mg}^{2+}$  and suppresses intestinal  $\text{Mg}^{2+}$  absorption. H: Hydrogen.

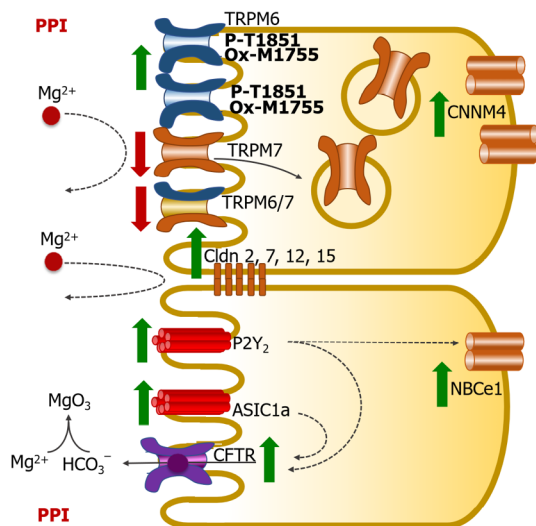


**Figure 5 P2Y<sub>2</sub> purinoceptors modulate intestinal magnesium absorption.**

Activation of P2Y<sub>2</sub> purinoceptor stimulates luminal cystic fibrosis transmembrane conductance regulator and basolateral  $\text{Na}^+\text{-HCO}_3^-$  cotransporter-1 (NBCe1) activities through a phospholipase C (PLC)-dependent mechanism. Active cystic fibrosis transmembrane conductance regulator (CFTR) and  $\text{Na}^+\text{-HCO}_3^-$  cotransporter-1 induce mucosal bicarbonate ( $\text{HCO}_3^-$ ) secretion, which reduces luminal free magnesium ( $\text{Mg}^{2+}$ ) and suppresses  $\text{Mg}^{2+}$  absorption.  $\text{Ca}^{2+}$ : Calcium; H: Hydrogen; K: Potassium;  $\text{Na}^+$ : Sodium.

PPI-induced small intestinal MBS (Figure 6) has been reported in humans[64], PPIH rats[11], and PPI-treated Caco-2 monolayers[35,53]. PPIs have also been shown to significantly increase ASIC1a and P2Y<sub>2</sub> expression in PPI-treated epithelium[35,53]. Active ASIC1a and P2Y<sub>2</sub> trigger MBS. Higher secreted bicarbonate in PPIH small intestines reduces free soluble  $\text{Mg}^{2+}$ , which disrupts  $\text{Mg}^{2+}$  absorption (Figure 6). Inhibition of MBS significantly increases duodenal  $\text{Mg}^{2+}$  absorption in PPIH rats[11].

In addition to the change in magnesiotropic protein expression and function and MBS, PPIs have been shown to induce structural change in the absorptive epithelium of the small intestine[58]. Prolonged PPI administration markedly decreased the villous length and absorptive area in the duodenal, jejunal, and ileal epithelium of PPIH rats. The underlying mechanism involves Paneth cell dysfunction in the small intestine[58]. Paneth cells have an important role in host-microorganism homeostasis in the small intestine by providing antimicrobial  $\alpha$ -defensin peptides[65,66]. Disruption of the secretory function of Paneth cells leads to infection and chronic inflammation of the small intestine [65,66]. In PPIH rats, a reduction in secretory granules and metaplasia of Paneth cells occurs in the duodenum, jejunum, and ileum, suggesting Paneth cell secretory dysfunction[58]. Chronic inflam-



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**Figure 6 Mechanism of proton pump inhibitor-suppressed small intestinal magnesium absorption in proton pump inhibitor-induced hypomagnesemia rats.** Proton pump inhibitor (PPI) suppresses membrane transient receptor potential melastatin 7 homodimer channel (TRPM7) and transient receptor potential melastatin 6/7 homodimer channel (TRPM6/7) expression but increases membrane transient receptor potential melastatin 6 homodimer channel (TRPM6) and cystathionine  $\beta$ -synthase domain divalent metal cation transport mediator 4 (CNRM4) expression. PPI induces phosphorylation of the T1851 residue and oxidation of the M1755 residue of the membrane TRPM6 channel, which reduces their channel permeability. These PPI effects reduce transcellular magnesium ( $Mg^{2+}$ ) absorption. Overexpression of claudin 2 (Cldn2), claudin 7 (Cldn7), claudin 12 (Cldn12), and claudin 15 (Cldn15) reduces paracellular permeability, which suppresses paracellular  $Mg^{2+}$  absorption. PPI also enhances  $P2Y_2$ - and acid-sensing ion-channel 1a (ASIC1a)-suppressed intestinal  $Mg^{2+}$  absorption. CFTR: Cystic fibrosis transmembrane conductance regulator;  $HCO_3^-$ : Bicarbonate; NBCe1:  $Na^+HCO_3^-$  cotransporter-1.

mation in the small intestinal epithelium leads to villous atrophy and reduction of the absorptive area in the small intestine of PPIH rats[58].

### Gut microbiota

The potential role of gut microbiota in colonic  $Mg^{2+}$  absorption has previously been proposed[36]. However, it is currently unknown how the small intestinal microbiome affects small intestinal  $Mg^{2+}$  absorption. Previous studies have shown that the small intestine is colonized by a complex gut microbiota community and is less numerous and diverse (approximately  $10^3$ – $10^7$  microbial cells/gram) than in the colon (approximately  $10^{12}$  microbial cells/gram)[67]. The dominant bacterial phyla in the small intestine are *Streptococcus* sp., *Lactobacillaceae*, and *Enterobacteriaceae*, whereas in the colon, the dominant phyla are *Bacteroidaceae*, *Prevotellaceae*, *Rikenellaceae*, *Lachnospiraceae*, and *Ruminococcaceae*[68, 69]. Prolonged PPI treatment can lead to gut microbiota dysbiosis, such as the reduction of *Actinobacteria* and *Bifidobacteria* spp., which are responsible for maintaining the mucosal barrier function[68].

Furthermore, long-term treatment with PPIs causes small intestinal bacterial overgrowth because of the loss of the gastric acid defensive barrier[70]. The jejunal samples of small intestinal bacterial overgrowth patients regularly showed increased production of toxic agents, such as serum endotoxin and bacterial compounds that stimulate the secretion of proinflammatory cytokines[71]. Apart from these findings, our previous study showed Paneth dysfunction and chronic inflammation in the small intestine of PPIH rats[58]. From the perspective of relevant gut microbiota, Paneth cell defects have been found to be associated with increased *Bacteroidetes* and *Enterococcus* and decreased *Bifidobacterium*[72], whereas *Bifidobacterium longum* has been found to promote cell proliferation and expression of *Lgr5* and *Wnt3a* in intestinal organoids and alleviate microbiota dysbiosis by regulating the functions of Paneth cells[73]. It is also possible that the synthesis of gut microbiota metabolites could lead to changes in the absorptive surface in the gut and/or stimulate gene expression[74].

In the colon, bifidobacterial fermentation leads to acidification of the colon, which shows beneficial absorption of  $Mg^{2+}$ [9,61,75]. In humans, small intestinal microbiota can also ferment the available carbohydrates and induce intestinal acidification[76]. In the human small intestine, a dominant bacterial phylum is *Streptococcus* sp.[77,78], which is an anaerobe that can ferment relatively simple carbohydrates at a high rate[79]. According to the above, luminal acidity markedly induces small intestinal  $Mg^{2+}$  absorption. Therefore, small intestinal fermentation should induce small intestinal  $Mg^{2+}$  absorption.

## CONCLUSION

Bulk absorption of digested  $Mg^{2+}$  occurs in the small intestine through transcellular active and

paracellular passive mechanisms. PTH, FGF-23, luminal protons, ASIC1a, OGR1, P2Y<sub>2</sub>, PPIs, and the microbiome have recently been proposed as regulatory factors of small intestinal Mg<sup>2+</sup> uptake. However, the regulatory mechanism of small intestinal Mg<sup>2+</sup> requires additional extensive studies.

## FOOTNOTES

**Author contributions:** Chamniansawat S wrote the manuscript; Suksridechacin N wrote the manuscript; Thongon N wrote and edited the manuscript.

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