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Hyperosmolarity evokes histamine release from ileum mucosa by stimulating a cholinergic pathway

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ABSTRACT

Changes in extracellular osmolarity lead to alteration in cellular volume. In the study, we examined the effects of hyperosmolarity on short-circuit currents (*Isc*) in the rat ileum using the Ussing chamber technique. Mucosal exposure to 20 mM glucose evoked a decrease of I_{SC} in the rat ileum, which was antagonized by the stretch-activated channel blocker GdCl3, TTX and atropine, respectively. In contrast, it was not blocked by phlorizin, a Na^+-glucose cotransporter SGLT1 inhibitor. Furthermore, the unabsorbed substances, such as sucrose, lactulose or urea, also induced a decrease of I_{SC} in rat ileum. ELISA results revealed that 20 mM glucose stimulated the release of histamine from rat ileum mucosa, which was attenuated by TTX. In addition, the glucose-induced I_{SC} was depressed by pyrilamine, a histamine H_1 receptor blocker (H_1 antagonist) whereas it was not affected by ranitidine (H_2 antagonist), clobenpropit (H_3 antagonists) or JNJ7777120 (H_4 antagonist), respectively. The ion substitution experiments suggest that the changes of Na^+ and HCO_3^- ion flux underlie the glucose-induced I_{SC}. In conclusion, osmotic stimulus decreased the basal I_{SC} of rat ileum by evoking histamine release from ileum mucosa. The changes of Na^+ and HCO_3^- ion transport are involved in the glucose-evoked decrease of basal I_{SC}.

1. Introduction

The intestinal epithelium is one of the first interfaces between the organism and the environment. During clinical manifestation, it delivers a selective permeable barrier that causes limitations to the permeability of luminal noxious molecules, for example toxins, pathogens and antigens, while permitting the necessary absorption of nutrients and water since maintenance of cell volume is crucial for this selective barrier. Disturbances in tonicity (effective osmolarity) are the major clinical disorders affecting cell volume [1]. Cell shrinking, secondary to hypertonicity, causes severe clinical manifestations and even death [2]. To date, there are several unresolved aspects of cell volume regulation. These include the identity of the structure of the osmotic sensor, and the nature of signaling pathways of the hypothetical cell volume sensor which leads to activation of volume-dependent ion transporters. It has been reported that hypertonicity stimulates Cl^- transport in eel intestinal epithelium by the activation of the luminal Na^+-K^+-$2Cl^-$ cotransporter (NKCC) and the functionality of basolateral Cl^- channels [3]. The present study reveals a new signaling pathway of cell volume regulation. We demonstrated that hyperosmolarity evoked histamine release from ileum mucosa, and then regulated Na^+ and HCO_3^- transport to alter cell volume.

2. Materials and methods

2.1. Animals and tissue preparation

All prospective procedures throughout the experiment were followed by protocol and conducted with the procedures for the Care and Use of Laboratory Animals of Shandong University, and the work was approved by the Medical Ethics Committee for

Abbreviations: I_{SC}, short-circuit current; TTX, tetrodotoxin; NKCC, Na^+-K^+-$2Cl^-$ cotransporter; ENS, enteric nervous system; ACh, acetylcholine; PLC, phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; NO, nitric oxide; AC, adenylyl cyclase.

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Experimental Animals, Shandong University, China (number ECAESDUSM 2012029). The usage of adult male Wistar rats ranging between 200 and 250 g were employed in this study. This specie of rat was acquired from the Animal Center of Shandong University, China. Animals were allocated and allowed free access to water, had been fasted overnight prior before experiments and were then anesthetized and decapitated. Tissue preparations were done according to the previously described procedures [4]. After eliminating luminal contents smoothly, the segments of the ileum were chopped along the mesenteric border and tissues were pinned flat on a Sylgard-lined petri dish with the mucosal surface facing down. The serosa and muscularis were removed gently and precisely in order to get mucosal-submucosal preparations. Tissue preparations were unremittingly oxygenated with a gas mixture (95% O_2 and 5% CO_2) while being bathed in ice-cold Krebs solution during preparation. The composition of Krebs solution was (in mM): 120.6 NaCl, 5.9 KCl, 2.5 $CaCl_2$, 1.2 KH_2PO_4, 1.2 $MgCl_2$, 15.4 $NaHCO_3$ and 11.5 Glucose.

2.2. Short-circuit current (I_{SC}) measurement

I_{SC} in vitro was measured using Ussing Chamber techniques. The tissue preparations were attached and placed between 2 halves of the Ussing Chambers. The exposed area (about 0.50 cm^2) was fortified with water-jacketed gas lifts which were then bathed on both sides with 5 mL Krebs solution and oxygenated with a gas mixture of 95% O_2 and 5% CO_2, while maintaining the pH at 7.4.

The Krebs solution was maintained at 37 °C and circulated through a reservoir. The tissue was then continuously voltage-clamped to a zero potential difference by using an external current with compensation for fluid resistance in consideration. The baseline value of the electrical parameters was measured as the mean over the 3 min interval immediately prior to administration of drug. The tissue was then equilibrated under these stated conditions for 20 min to maintain the I_{SC} proceeding to the addition of drugs. The transepithelial potential difference for each prospective preparation was calculated with Ag/AgCl reference electrodes (P2020S; Physiologic Instruments, San Diego, Calif) connected to a preamplifier that was in turn connected to a voltage clamp amplifier (VCC MC4; Physiologic Instruments, San Diego, Calif). The changes in the short circuit current (ΔI_{SC}) were calculated, and results were recorded on the basis of the value before and after the process of stimulation. The ΔI_{SC} was normalized as the current per unit area of epithelium ($\mu A/cm^2$). The viability of tissues was checked by inducing stimulation by acetylcholine (ACh).

2.3. Measurement of histamine

The ileum mucosa was attached between the 2 halves of the Ussing chambers (0.50 cm^2). The tissues were there after bathed on both sides with 5 mL Krebs solution, gassed with 95% O_2 and 5% CO_2, pH adjusted to 7.4 and maintained persistently at 37 °C by circulating the solution of contents via a reservoir throughout the experiments. Glucose (20 mM) was added to the mucosa side solution then the tissues were taken out and homogenized and centrifuged for ELISA at 4 °C. Histamine was measured using a Histamine ELISA Kit for mouse (R&D, USA) with a detection range from 0.5 to 200.0 ng/mL. The histamine standard curve was calculated using a 4-PL curve fit ($R^2 = 0.9950$).

2.4. Drugs

The D-glucose (20 mM), phlorizin (100 μM), D (+)-Sucrose (20 mM), lactulose (20 mM) or saccharin (1 mM) was added to the mucosal side bathing solution and measured the changes of I_{SC}. Atropine (10 μM) was used to block the cholinergic system. $GdCl_3$ (100 μM) was used to block the osmotic sensors. Histamine receptor antagonists including pyrilamine (H_1 antagonist,1 μM), ranitidine (H_2 antagonist,1 μM), clobenpropit (H_3 antagonist,1 μM) or JNJ7777120 (H_4 antagonist,1 μM) was added to serosal side bathing solution to study the effect of histamine to the hyperosmolarity. Tetrodotoxin (TTX,1 μM) was used to block the neural pathway. Atropine, TTX or furosemide (100 μM) was added to the serosal side bathing solution. In the alternative experiments, the Cl^- free solution contained (in mM): 117 Na-gluconate, 4.7 K-gluconate, 8 Ca-(gluconate)$_2$, 1.2 Mg-(gluconate)$_2$,1.2 NaH_2PO_4, 25 $NaHCO_3$, and 11 glucose. In HCO_3^--free solution. HCO_3^- was replaced by gluconate and HEPES buffer and the pH were adjusted to 8.0. In Na^+-free solution, 120.6 mM NaCl was replaced by 120.6 mM KCl, pH 7.4 adjusted with KOH.

2.5. Data analysis and statistics

Data showed as means ± SEM and the n values represent the numbers of animals used in these experiments. We considered one-way ANOVA or unpaired Student's *t*-tests to investigate if there were significant differences in basal electrical parameters among the tissue elements. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Osmotic stimulus evoked a decrease in I_{SC} in rat ileum

It's well known the absorption of glucose in intestinal epithelium causes an increase of I_{SC} because of Na^+ co-transport. Our experiments confirmed that indeed, the addition of glucose (20 mM) to mucosal bathing solution suggested an increase in I_{SC} in rat jejunum (Fig. 1A). In contrast, 20 mM glucose evoked a decrease of I_{SC} in the rat ileum (Fig. 1B). The absorption of glucose in intestinal epithelium is through Na + -glucose cotransporter SGLT1 therefore absorption of glucose is Na + -dependent. Since phlorizin inhibits SGLT1, we added phlorizin to test whether the change in *Isc* is evoked by SGLT1. Phlorizin blocked glucose-evoked increase of I_{SC} in jejunum, however, did not exert any effect on glucose-evoked decrease of I_{SC} in the rat ileum (Fig. 1C). Furthermore, sucrose or lactulose which is not absorbed by the small intestine also caused a decrease of I_{SC} (Fig. 1D and E). In addition, a non-nutrient osmotic load such as urea (20 mM) showed similar result (Fig. 1F). It is well known that the small intestine expresses sweet taste receptors [5,6]. To elucidate the role of sweet taste receptors, saccharin (1 mM), a sweet taste receptor agonist was used. However, it had no effect on the I_{SC} of the ileum mucosa (Fig. 1G). Notably, the stretch-activated channel blocker $GdCl_3$ (100 μM) largely attenuated the osmotic stimulus-evoked I_{SC} in the rat ileum (Fig. 1H). These results suggest that 20 mM glucose-induced I_{SC} in the rat ileum may be due to the hyperosmotic challenges.

3.2. The osmotic stimulus-evoked I_{SC} in the rat ileum is mediated by the cholinergic circuitry of enteric nervous system (ENS)

The ENS plays a significant part in the regulation of intestinal epithelial ion transport. The principal role of submucousal plexus is in sensing the environment within the lumen. To examine the contribution of the ENS in the effects of hypertonic challenge, TTX (10^{-6} M) was added to the serosal bathing solution to block the ENS. In the presence of TTX, the 20 mM glucose-induced I_{SC} was almost suppressed (Fig. 2A). Interestingly atropine, a selective muscarinic ACh receptor antagonist also inhibited the effect of 20 mM glucose on the I_{SC} of ileum mucosa (Fig. 2B).

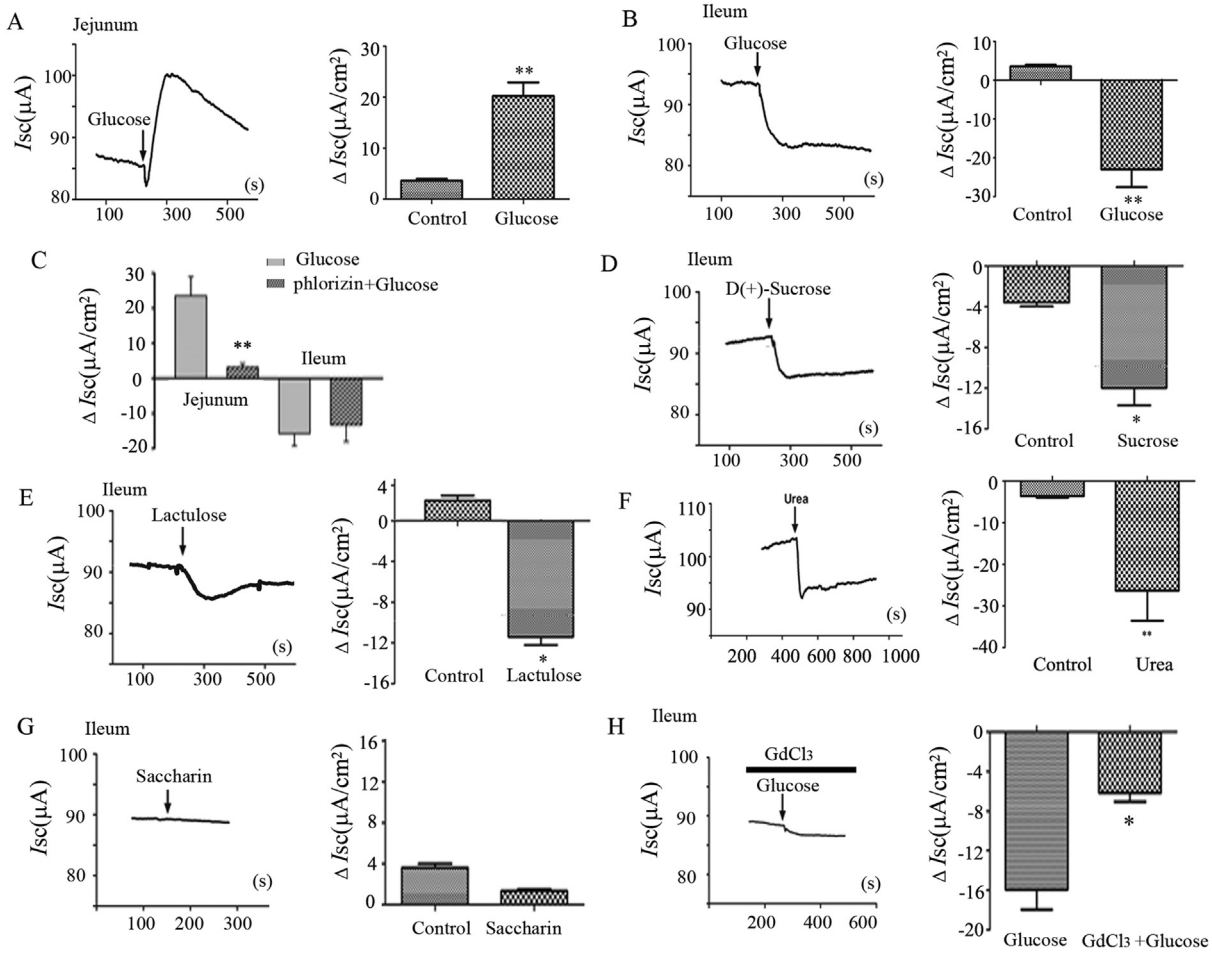

Fig. 1. Osmotic stimulus evoked a decrease in I_{SC} in rat ileum.
Adding a relatively high concentration of glucose (20 mM) to mucosal bathing solution evoked an increase of I_{SC} in rat jejunum (A), but stimulated a decrease of I_{SC} in rat ileum(B). Phlorizin, a non-selective SGLT inhibitor, blocked glucose-evoked increase of I_{SC} in jejunum, however, did not exert any effect on glucose-evoked decrease of I_{SC} in rat ileum(C). Like glucose, sucrose or lactulose also caused a decrease of I_{SC} (D and E). In addition, urea (20 mM), a non-nutrient osmotic substance, evoked a decrease of I_{SC} in rat ileum either (F). Saccharin (1 mM), a sweet taste receptor agonist, had no effect on the I_{SC} of ileum mucosa (G). Notably, the stretch-activated channel blocker $GdCl_3$ (100 μM), largely attenuated the osmotic stimulus-evoked I_{SC} in rat ileum(H). $n = 7$; *, $P < 0.05$; **, $P < 0.01$versus Control or glucose.

3.3. Histamine H_1 receptor involves in hyperosmotic solution-evoked I_{SC}

The ELISA results confirmed that 20 mM glucose stimulated histamine release from the ileum mucosa which was inhibited by pretreatment with TTX (10^{-6} M) (Fig. 3A). Furthermore, pyrilamine (10^{-6} M), an antagonist of histamine H_1 receptor markedly inhibited the 20 mM glucose-induced I_{SC} (Fig. 3B and F) whereas ranitidine (H_2 antagonist), clobenpropit (H_3 antagonists) or JNJ7777120 (H_4 antagonist) which did not inhibit (Fig. 3C-F).

3.4. HCO_3^- and Na^+ are involved in the glucose-induced decrease of Isc

In order to find which ion involves in the glucose-induced decrease of *Isc*, Na^+, Cl^- and HCO_3^- was removed from the bathing solution, respectively. Either HCO_3^--free or Na^+-free Krebs solution largely reduced the change of *Isc* in response to hypertonicity (Fig. 4A1 and A2). But Cl^--free Krebs solution which did not (Fig. 4A3 and A4).

In addition, the hypertonicity-evoked response was not inhibited by furosemide (100 μM), an antagonist of NKCC (Fig. 4B).

4. Discussion

We reported here that osmotic stimulus evoked a response in I_{SC} measured by Ussing Chamber technique which was mediated by histamine released from ileum mucosa through the reflex pathway. Further study confirmed Na^+ and HCO_3^- ion involved hyperosmotic-induced I_{SC} in the rat ileum mucosa.

In the present study, we found that 20 mM glucose evoked an inward current in the rat ileum mucosa whereas induced an outward current in the rat jejunum. It's well known that the absorption of glucose in intestinal epithelium is Na^+-dependent. Therefore, the absorption of glucose in intestinal epithelium causes an increase of I_{SC}. Indeed, the glucose-evoked increase of I_{SC} in the rat jejunum was totally blocked by phlorizin, a Na^+-glucose co-transporter inhibitor. Interestingly glucose evoked a decrease of basal I_{SC} in the rat ileum which is not consistent with previous studies [7,8]. They identified a 20 mM glucose-evoked elevation in ileal *Isc* of either rat or mouse. Boudry et al. also demonstrated positive glucose-induced currents in both the jejunum and porcine ileum [9]. It is well known that glucose is absorbed mainly in proximal small intestine. An increase of *Isc* represents increased SGLT1 activity. Notably, SGLT1 blocker phlorizin did not affect the glucose-evoked decrease of I_{SC}

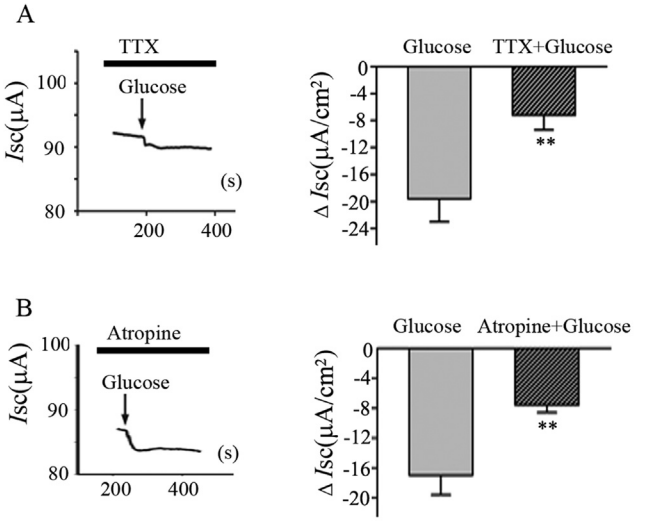

Fig. 2. The osmotic stimulus-evoked I_{SC} in rat ileum is mediated by the cholinergic circuitry of enteric nervous system (ENS).
Serosal application of TTX (10^{-6} M) markedly attenuated the 20 mM glucose-induced I_{SC} (A). Atropine, a M-receptor antagonist, also suppressed the 20 mM glucose-evoked effect (B). $n = 5$; **, $P < 0.01$versus glucose.

in the rat ileum, which suggests that the absorption of glucose is not involved in the change of I_{SC} in the rat ileum. The data that some unabsorbed carbohydrates, such as sucroses, lactulose or urea also evoked a decrease of I_{SC} in the rat ileum further proves that electrogenic Na^+-glucose cotransporter is not involved in the basal decrease in I_{SC}.

Undoubtedly these unabsorbed substances used in our study can cause an increase in osmotic pressure of the intestinal lumen. As expected, $GdCl_3^+$, a stretch-activated channel blocker significantly inhibited the glucose-evoked response.

It is noteworthy that the glucose-induced response was inhibited either by TTX or ACh receptor antagonist atropine. Therefore we predict that the glucose-evoked response in the rat ileum is mediated through cholinergic neurotransmission. Notably, the hypertonic challenge stimulated the release of histamine. Histamine is a type of transmitter in the nervous system and a signaling molecule in the skin, the gut and the immune system [10].

It's well known that the histamine can be released from mast cells [11]. Hyperosmolar stimulation evokes histamine release from mast cells [12]. It has been demonstrated that mast cells are innervated by submucosal neurons [13–15], and 10-15% of intestinal mucosal mast cells contacted vagal nerve terminals [16]. Mannaioni et al. reported that ACh evoked histamine secretion

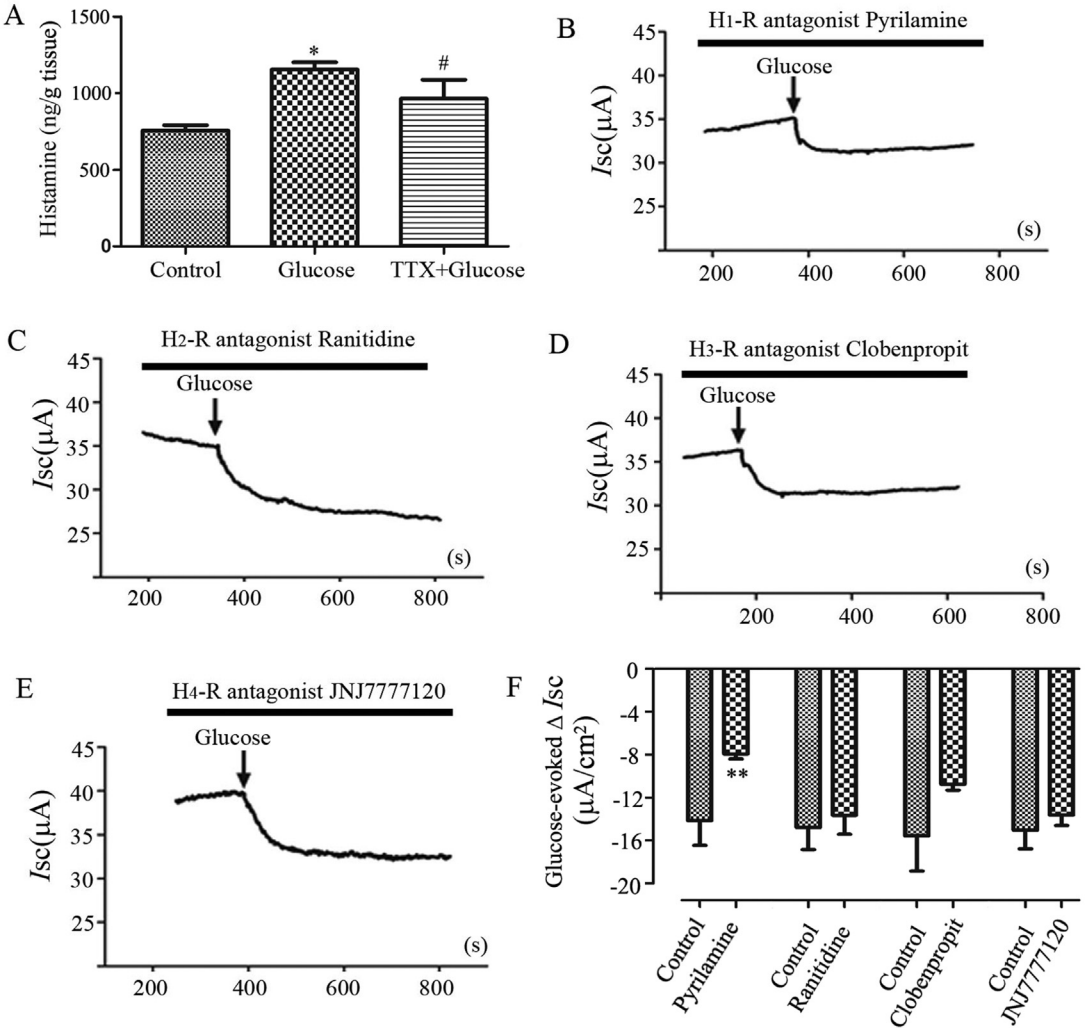

Fig. 3. Histamine H_1 receptor involves in hyperosmotic solution-evoked I_{SC}.
ELISA results showed that histamine was release from ileum mucosa in the presence of glucose, which was inhibited by co-incubation of TTX (10^{-6} M)(A). Pyrilamine (10^{-6} M), an antagonism of histamine 1 receptor (H_1R), largely inhibited osmotic stimulus-evoked response (B,F). However, the ranitidine (H_2R antagonist), clobenpropit (H_3R antagonist) or JNJ7777120 (H_4R antagonist) had no obvious influence (C-F). $n = 8$; *, $P < 0.05$; **, $P < 0.01$versus Control. # $P < 0.05$ versus glucose.

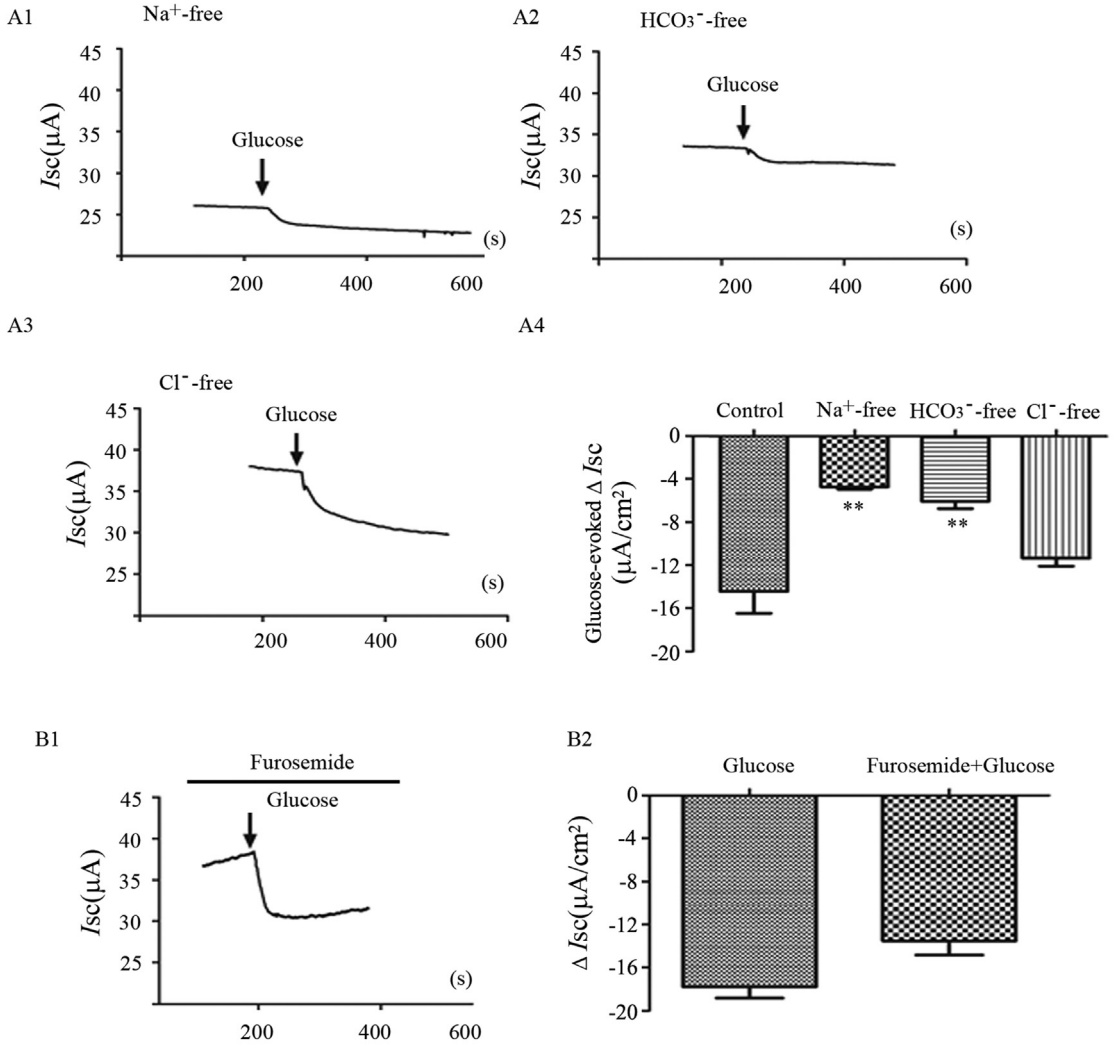

Fig. 4. The ions flux underlying the decrease of I_{SC} is mainly Na^+ and $HCO3^-$.
Na^+, Cl^- or HCO_3^- was removed from the bathing solution, respectively. Either HCO_3^--free or Na^+-free Krebs solution largely reduced the change of *Isc* in response to hyperosmotic stimulus (A1 and A2), whereas Cl^--free Krebs solution did not (A3,A4). Moreover, mucosal application of furosemide (100 μM), a blocker of NKCC, had no effect on hyperosmotic-evoked *Isc* (B1,B2). $n = 10$; **, $P < 0.01$ versus Control.

from rat mast cells, which was competitively blocked by atropine [17,18]. Therefore, we deduced that hyperosmotic solution stimulates submucosal cholinergic nerve fiber, and then triggers histamine release from mast cells, which is confirmed by the data of the effect of pyrilamine, an antagonist of histamine H_1 receptor or ELISA results. The histamine H_1R-H_4Rs have been found in enteric neurons in the whole intestine and ENS in humans [19]. The histamine H_1 receptor are also presented on epithelial cells in both the small and large intestine to alter chloride secretion in rat [20,21]. In our present study, the histamine H_1 receptor antagonist blocked the glucose-evoked I_{SC} in rat ileum. But, chloride is not involved in hyperosmotic-evoked response in I_{SC}. Strikingly, bilateral removal of Na^+ or HCO_3^- obviously inhibited the hyperosmotic-evoked I_{SC}.

In summary, based on the findings of the present study, authors would like to report for the first time that hyperosmotic stimulus decreased the basal *Isc* of the rat ileum by evoking histamine release which induces the changes of Na^+ and $HCO3^-$ ion flux in intestinal epithelial cells.

Competing interests

None.

Contributors

Study concept and design: B W, N A and D Z. Acquisition of data: B W, N A, H W,L X and H L. Analysis and interpretation of data: N A, H W and D Z. Drafting of the manuscript: N A, A S S and D Z. Statistical analysis: N A and J L. Revision of the manuscript: A S S. Approved final version of manuscript: all authors.

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