

## Basic Study

## Effect of gingerol on colonic motility *via* inhibition of calcium channel currents in rats

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### Abstract

**AIM:** To investigate the effect of gingerol on colonic motility and the action of L-type calcium channel currents in this process.

**METHODS:** The distal colon was cut along the mesenteric border and cleaned with Ca<sup>2+</sup>-free physiological saline solution. Muscle strips were removed and placed in Ca<sup>2+</sup>-free physiological saline solution, which was oxygenated continuously. Longitudinal smooth muscle samples were prepared by cutting along the muscle strips and were then placed in a chamber. Mechanical contractile activities of isolated colonic segments in rats were recorded by a 4-channel physiograph. Colon smooth muscle cells were dissociated by enzymatic digestion. L-type calcium currents were recorded using the conventional whole-cell patch-clamp technique.

**RESULTS:** Gingerol inhibited the spontaneous contraction of colonic longitudinal smooth muscle in a dose-dependent manner with inhibition percentages of 13.3% ± 4.1%, 43.4% ± 3.9%, 78.2% ± 3.6% and 80.5% ± 4.5% at 25 μmol/L, 50 μmol/L, 75 μmol/L

and 100  $\mu\text{mol/L}$ , respectively ( $P < 0.01$ ). Nifedipine, an L-type calcium channel blocker, diminished the inhibition of colonic motility by gingerol. Gingerol inhibited L-type calcium channel currents in colonic longitudinal myocytes of rats. At a 75  $\mu\text{mol/L}$  concentration of gingerol, the percentage of gingerol-induced inhibition was diminished by nifedipine from  $77.1\% \pm 4.2\%$  to  $42.6\% \pm 3.6\%$  ( $P < 0.01$ ). Gingerol suppressed  $I_{\text{Ba}}$  in a dose-dependent manner, and the inhibition rates were  $22.7\% \pm 2.38\%$ ,  $35.77\% \pm 3.14\%$ ,  $49.78\% \pm 3.48\%$  and  $53.78\% \pm 4.16\%$  of control at 0 mV, respectively, at concentrations of 25  $\mu\text{mol/L}$ , 50  $\mu\text{mol/L}$ , 75  $\mu\text{mol/L}$  and 100  $\mu\text{mol/L}$  ( $P < 0.01$ ). The steady-state activation curve was shifted to the right by treatment with gingerol. The value of half activation was  $-14.23 \pm 1.12$  mV in the control group and  $-10.56 \pm 1.04$  mV in the 75  $\mu\text{mol/L}$  group ( $P < 0.05$ ) with slope factors,  $K_s$ , of  $7.16 \pm 0.84$  and  $7.02 \pm 0.93$  ( $P < 0.05$ ) in the control and 75  $\mu\text{mol/L}$  groups, respectively. However, the steady-state inactivation curve was not changed, with a half-inactivation voltage, 0.5 V, of  $-27.43 \pm 1.26$  mV in the control group and  $-26.56 \pm 1.53$  mV in the 75  $\mu\text{mol/L}$  gingerol group ( $P > 0.05$ ), and a slope factor,  $K$ , of  $13.24 \pm 1.62$  in the control group and  $13.45 \pm 1.68$  ( $P > 0.05$ ) in the 75  $\mu\text{mol/L}$  gingerol group.

**CONCLUSION:** Gingerol inhibits colonic motility by preventing  $\text{Ca}^{2+}$  influx through L-type calcium channels.

**Key words:** Gingerol; Colonic motility; L-type calcium channel current; Spontaneous contraction; Longitudinal smooth muscle myocytes

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**Core tip:** Gingerol, a non-pungent molecule, has an inhibitory effect on colonic motility. There are many ion channels and second messengers involved in this process; however, no reports have described the effects of gingerol on L-type calcium channel currents. In the present study, we found that 6-gingerol obviously inhibited spontaneous contraction of longitudinal smooth muscle by preventing  $\text{Ca}^{2+}$  influx through L-type calcium channels.

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## INTRODUCTION

Ginger, the rhizome of *Zingiber officinale* Roscoe, and its components have various pharmacological

actions, including anti-inflammatory, anti-cancer, anti-oxidant, anti-platelet, anti-aggregation, anti-fungal, anti-constipation and anti-diarrheal activities<sup>[1-6]</sup>. The chemical constituents of ginger rhizomes are volatile and non-volatile pungent phytochemicals and include the biologically active components, gingerols, shogaols, paradols and zingerone<sup>[7,8]</sup>.

Gingerol, a non-pungent component, has an inhibitory effect on colonic motility. Iwami *et al*<sup>[9]</sup> reported that gingerol can inhibit colonic motility without adverse effects on small intestinal motility and the cardiovascular system. The non-pungent property of gingerol makes it useful as an oral or suppository medicine for treating diarrhea and other gastrointestinal disorders<sup>[10,11]</sup>. Abnormal facilitation of gastrointestinal motility and excessive fluid secretion of the gastrointestinal tract cause diarrhea. There are many ion channels and second messengers involved in this process; however, no reports have described the effects of gingerol on L-type calcium channel currents. The purpose of the present study was to clarify the effect of gingerol on colonic motility and the role of L-type calcium channel currents in this process.

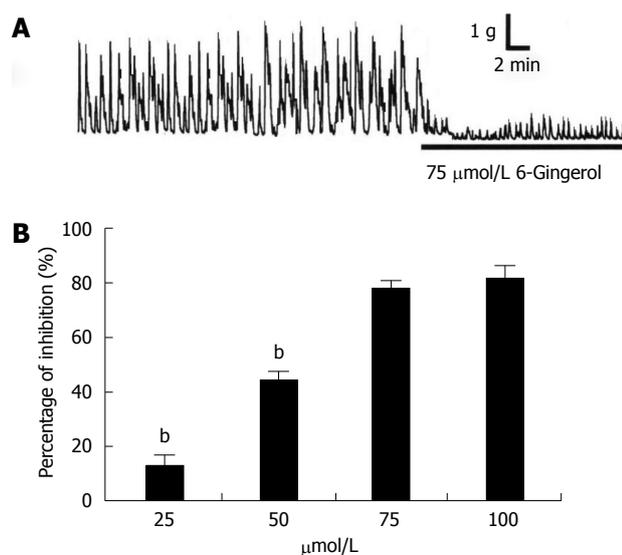
## MATERIALS AND METHODS

### Experimental animals

Male Wistar rats (weighing  $250 \pm 50$  g) were purchased from the Experimental Animal Center of Dalian Medical University. They were maintained in plastic cages at  $23 \pm 2^\circ\text{C}$  and a relative humidity of  $55\% \pm 2\%$  under standard conditions with a 12-h light/dark cycle (light: 7:00 AM to 7:00 PM) for 1 wk prior to performing the experiments. The experiments were approved by the Animal Care and Use Committee of Dalian Medical University.

### Preparation and contraction recording of smooth muscle strips

Male Wistar rats bred at the Experimental Animal Center of Dalian Medical University (Dalian, China) were anesthetized with ethyl ether prior to cervical exsanguination. The distal colon was cut along the mesenteric border and cleaned with  $\text{Ca}^{2+}$ -free physiological saline solution (PSS). Muscle strips (about  $3 \text{ mm} \times 10 \text{ mm}$ ) were removed and placed in  $\text{Ca}^{2+}$ -free PSS, which was oxygenated continuously. Following the careful removal of the mucosa and submucosa by dissection, smooth muscle strips were obtained. Longitudinal smooth muscle samples were prepared by cutting along the muscle strips and were then placed in a chamber. One end of the strip was fixed on the lid of the chamber by a glass claw, and the other end was attached to an isometric force transducer (TD-112S, Japan) to record contraction. The chamber (5 mL volume) was constantly perfused with pre-Tyrode's solution at 1 mL/min. The temperature of the chamber was maintained at  $37.0$



**Figure 1** Effect of 6-gingerol on spontaneous contraction of colonic longitudinal smooth muscle in rats. A: The original electrophysiological data of 6-gingerol on spontaneous contraction; B: The inhibitory effect of 6-gingerol on spontaneous contraction at different concentrations.  $n = 8$ ,  $^bP < 0.01$  vs consecutive high concentration group.

$\pm 0.5$  °C by a water bath thermostat (WC/09-05, Chongqing, China). The muscle strips were incubated for at least 40 min before beginning the experiments.

#### Preparation of cells

Colon smooth muscle cells (SMCs) were dissociated by enzymatic digestion. The colon tissue was pinned to the Sylgard surface of a Petri dish, and the mucosa was carefully dissected away under an anatomical microscope. The smooth muscle strips were then cut into small strips (2 mm  $\times$  2 mm), placed in 2 mL calcium-free PSS supplemented with 0.12% (w/v) collagenase (type II), 0.2% soybean trypsin inhibitor and 0.2% bovine serum albumin, and incubated for 20-30 min at 37 °C. The tissue pieces were rinsed in  $Ca^{2+}$  free PSS solution five times to remove the collagenase enzymes and were maintained at 4 °C for 6 h until use. Single SMCs were isolated by several gentle triturations through the tip of a free-polished Pasteur pipette.

#### Whole-cell patch clamp recordings

L-type calcium currents were recorded using the conventional whole-cell patch-clamp technique. Patch-clamp pipettes were manufactured from borosilicate glass capillaries (GC 150T-7.5, Clark Electromedical Instruments, London, United Kingdom) using a 2-stage puller (PP-83, Narishige, Tokyo, Japan). When filled with pipette solution, the resistance of the patch pipette was 3-5 M $\Omega$ . The isolated myocytes were transferred to a small chamber on the stage of an inverted microscope (IX-71 Olympus, Japan) for 10-15 min and were well-attached to the bottom of the chamber. Then, the chamber was continuously

superfused with PSS. An 8-channel perfusion system (L/M-sps-8, List Electronics, Germany) was used to change the perfusate. Whole-cell currents were recorded with an EPC-10 amplifier (EPC, Germany). All experiments were performed at room temperature (20-25 °C).

#### Drugs and solutions

Tyrode's solution contained the following (in mmol/L): 147 NaCl, 4 KCl, 1.05 MgCl<sub>2</sub>·6H<sub>2</sub>O, 0.42 CaCl<sub>2</sub>·2H<sub>2</sub>O, 1.81 Na<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O and 5.5 glucose. The  $Ca^{2+}$ -free PSS contained the following (in mmol/L): 134.8 NaCl, 4.5 KCl, 5 glucose and 10 HEPES; the pH was adjusted to 7.4 with Tris (hydroxymethyl) aminomethane. The modified K-B solution contained the following (in mmol/L): 50 L-glutamate, 50 KCl, 20 taurine, 20 KH<sub>2</sub>PO<sub>4</sub>, 3 MgCl<sub>2</sub>·6H<sub>2</sub>O, 10 glucose, 10 HEPES, and 0.5 egtazic acid (pH adjusted to 7.40 with KOH). The extracellular solution contained the following (in mmol/L): 127 NaCl, 5 TEA, 4 NaHCO<sub>3</sub>, 0.33 NaH<sub>2</sub>PO<sub>4</sub>, 10 HEPES, 1.8 MgCl<sub>2</sub>, 2 CaCl<sub>2</sub>, 10 glucose, and 5 Na<sub>2</sub>-pyruvate (pH adjusted to 7.4 with NaOH). The pipette solution contained the following (in mmol/L): 126 CsCl, 1 MgCl<sub>2</sub>, 10 HEPES, 3.1 Mg·ATP, 5 Na<sub>2</sub>-phosphocreatine, and 0.42 Li<sub>2</sub>·GTP; the pH was adjusted to 7.2 with CsOH. Nifedipine and gingerol were purchased from Sigma Chemical Co. (United States).

#### Statistical analysis

All data are expressed as mean  $\pm$  SD. The Duncan's multiple range test was used. Differences were considered to be significant at  $P$ -values of less than 0.05.

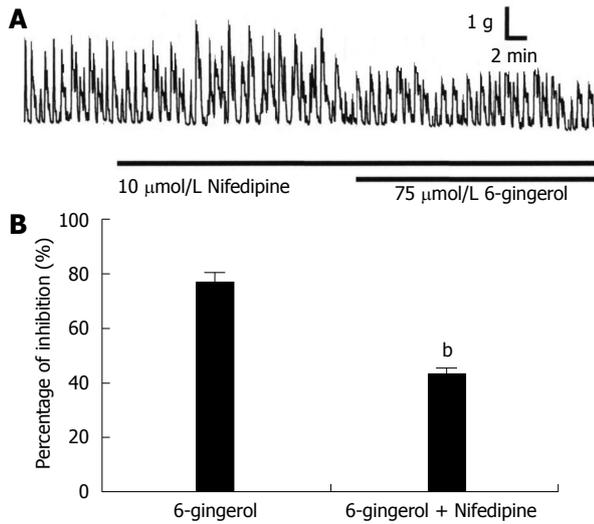
## RESULTS

#### Effect of gingerol on spontaneous contraction of colonic smooth muscle

Spontaneous contraction of the muscle strips usually appeared after approximately 40 min of incubation in Tyrode's solution. The effects of 75  $\mu$ mol/L gingerol on the spontaneous contraction of colonic longitudinal smooth muscle were observed. After administering gingerol, spontaneous contraction was significantly inhibited (Figure 1A,  $n = 8$ ). Different concentrations of gingerol obviously inhibited the spontaneous contraction of the muscle strips in a dose-dependent manner, with inhibition percentages of 13.3%  $\pm$  4.1%, 43.4%  $\pm$  3.9%, 78.2%  $\pm$  3.6% and 80.5%  $\pm$  4.5% at 25  $\mu$ mol/L, 50  $\mu$ mol/L, 75  $\mu$ mol/L and 100  $\mu$ mol/L, respectively (Figure 1B,  $n = 8$ ).

#### Effect of L-type calcium channel blocker on gingerol-induced inhibition of spontaneous contraction of colonic smooth muscle

To further investigate the mechanism of the gingerol-induced inhibition of spontaneous contraction, the effect of gingerol on gastric motility was observed



**Figure 2** Effect of nifedipine on gingerol-induced inhibition in rat colonic longitudinal smooth muscle. A: The original electrophysiological data of nifedipine on gingerol-induced inhibitory effects in longitudinal smooth muscle contraction; B: The statistical diagram of the inhibition.  $n = 6$ ,  $^bP < 0.01$  vs gingerol group.

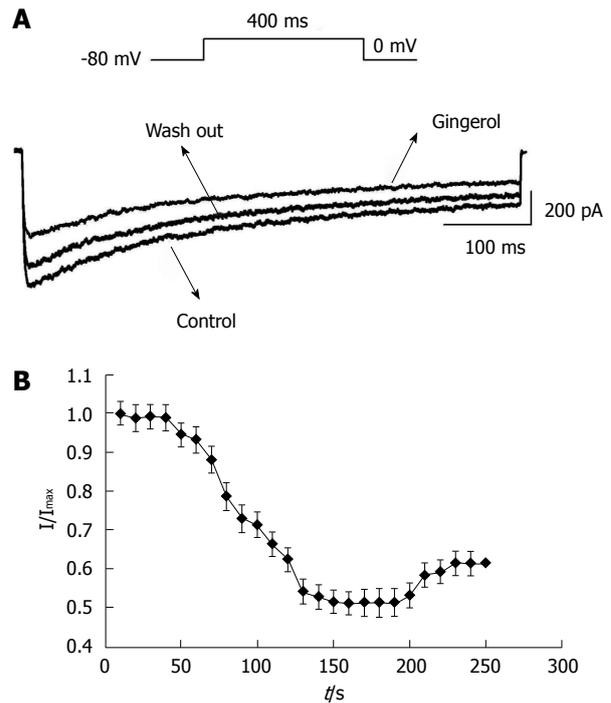
in the presence of nifedipine (10  $\mu\text{mol/L}$ ), an L-type calcium channel blocker. Nifedipine was found to diminish the gingerol-induced colonic motility inhibition. At a 75  $\mu\text{mol/L}$  concentration of gingerol, the percentage of gingerol-induced inhibition was diminished by nifedipine from  $77.1\% \pm 4.2\%$  to  $42.6\% \pm 3.6\%$  ( $P < 0.01$ ) (Figure 2,  $n = 6$ ).

#### L-type calcium channel current and $I_{Ba}$ in colonic longitudinal myocytes of rats

The membrane potential was clamped at -80 mV, and an  $I_{Ca}$  was elicited by a step voltage pulse from -60 mV to +60 mV for 400 ms at 10 s intervals. With an external solution containing 2 mmol/L  $\text{CaCl}_2$ , an L-type calcium current could be conducted under whole-cell configuration. The peak value of the L-type calcium current appeared at 0 mV, and turnover potential appeared between +50 mV and +60 mV. The amplitude of  $I_{Ca}$  was relatively small. After replacing 2 mmol/L  $\text{Ca}^{2+}$  with 10 mmol/L  $\text{Ba}^{2+}$  in the external solution, an  $I_{Ba}$  was elicited under the same stimulus modality. The shapes of the  $I_{Ca}$  and  $I_{Ba}$  I-V curves were the same. However, the amplitude of  $I_{Ba}$  was much larger than that of  $I_{Ca}$ . This indicates that  $I_{Ba}$  is a better carrier of  $\text{Ca}^{2+}$  than  $I_{Ca}$ .

#### Effect of gingerol on $I_{Ba}$

Under whole-cell configuration, the membrane potential was clamped at -80 mV, and an  $I_{Ba}$  was elicited by a single step command pulse from -80 to 0 mV for 400 ms at 10 s intervals. The time-course showed that  $I_{Ba}$  was immediately inhibited by the addition of gingerol (50 mmol/L), and within approximately 150 s this inhibitory effect had stabilized. The inhibitory percentage was 51.28%

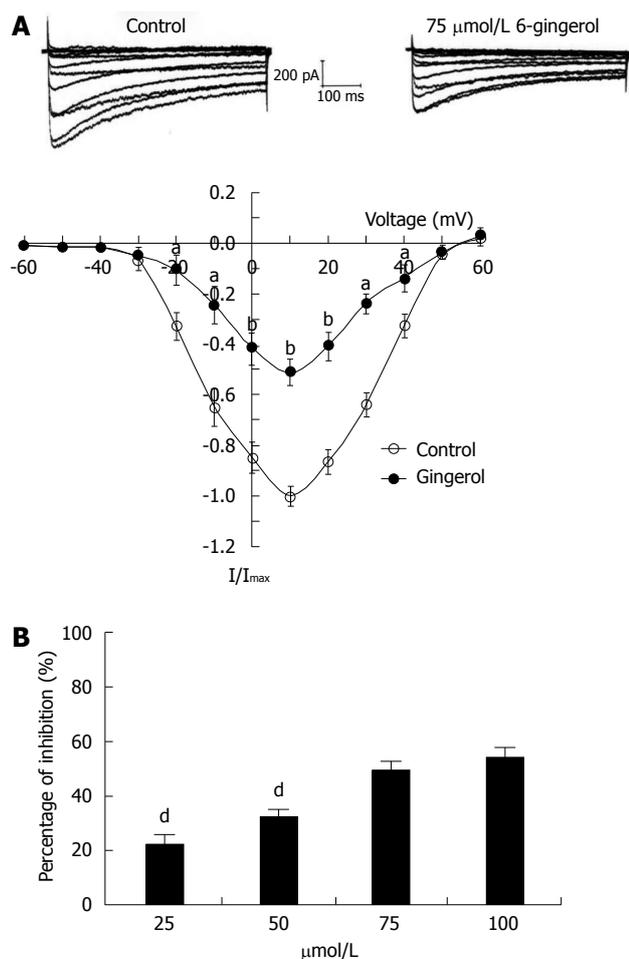


**Figure 3** Time dependency of the effect that 6-gingerol acts on  $I_{Ba}$  in colonic longitudinal smooth muscle in rats. A: Raw traces of  $I_{Ba}$  at 0 mV; B: Peak responses of  $I_{Ba}$  at 0 mV normalized and averaged for cells exposed to 6-gingerol.

$\pm 2.12\%$ , and  $I_{Ba}$  recovered partially after washout with normal control superfusing solution (Figure 3). Gingerol significantly decreased  $I_{Ba}$  in the I-V relation curve at every depolarized command step potential from -20 to +40 mV. Gingerol suppressed  $I_{Ba}$  in a dose-dependent manner, and the inhibition rates were  $22.7\% \pm 2.38\%$ ,  $35.77\% \pm 3.14\%$ ,  $49.78\% \pm 3.48\%$  and  $53.78\% \pm 4.16\%$  of control at 0 mV, respectively, at concentrations of 25  $\mu\text{mol/L}$ , 50  $\mu\text{mol/L}$ , 75  $\mu\text{mol/L}$  and 100  $\mu\text{mol/L}$  (Figure 4).

#### Effect of gingerol on steady-state inactivation and activation of $I_{Ba}$

A double-pulse protocol was used to measure the steady state inactivation of  $I_{Ba}$  as a function of membrane potential. Prepulse potentials ranging from -100 to +40 mV were applied for a duration of 3.75 s. Following a 7 ms interpulse interval at a potential of -60 mV, the membrane potential was raised to a test potential of 0 mV for 1 s. The currents were then normalized to the current obtained at -100 mV ( $I/I_{max}$ ) and plotted against each prepulse potential. The plotted data were well fitted by the Boltzmann equation, with a half-inactivation voltage, 0.5 V, of  $-27.43 \pm 1.26$  mV in the control group and  $-26.56 \pm 1.53$  mV in the 75  $\mu\text{mol/L}$  gingerol group ( $P > 0.05$ ,  $n = 6$ ), and a slope factor,  $K$ , of  $13.24 \pm 1.62$  in the control group and  $13.45 \pm 1.68$  ( $P > 0.05$ ) in the 75  $\mu\text{mol/L}$  gingerol group (Figure 5A). The steady-state activation curves were estimated from the peak



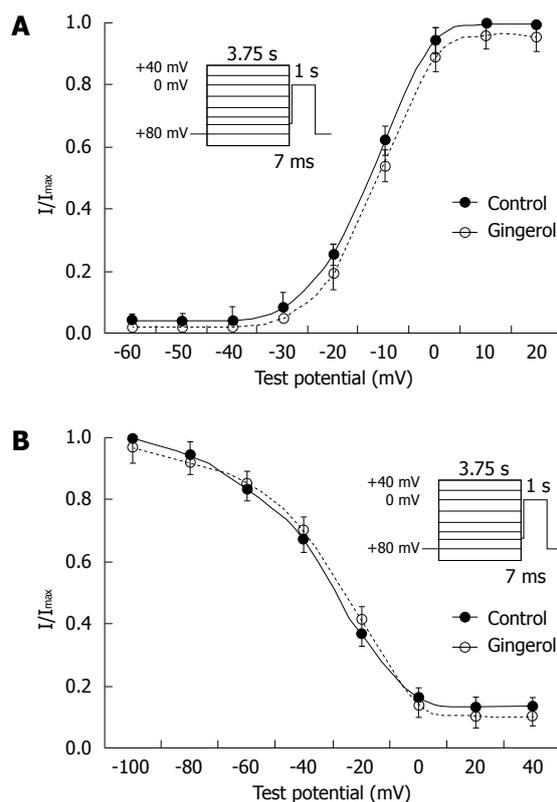
**Figure 4** Effect of 6-gingerol on  $I_{Ba}$  in colonic longitudinal smooth muscle in rats. A: Raw traces of  $I_{Ba}$  elicited by step pulse and I-V relationship of  $I_{Ba}$  when cell was exposed to 6-gingerol; B: The inhibitory effect of 6-gingerol at different concentrations.  $n = 8$ ,  $^{\#}P < 0.05$ ,  $^{\ast}P < 0.01$  vs control group;  $^{\ast}P < 0.01$  vs consecutive high concentration group.

conductance at each potential using the following equation:  $I_{Ba} = g_{Ba} (V - V_{rev})$ , where  $g_{Ba}$ ,  $V$  and  $V_{rev}$  are peak conductance, test potential and observed reversal potential, respectively. The value of half activation was  $-14.23 \pm 1.12$  mV in the control group and  $-10.56 \pm 1.04$  mV in the 75  $\mu\text{mol/L}$  group ( $P < 0.05$ ,  $n = 6$ ) with slope factors,  $K_s$ , of  $7.16 \pm 0.84$  and  $7.02 \pm 0.93$  ( $P < 0.05$ ) in the control and 75  $\mu\text{mol/L}$  groups, respectively (Figure 5B).

## DISCUSSION

In the present study, gingerol inhibited the spontaneous contraction of colonic longitudinal smooth muscle in a dose-dependent manner. Nifedipine (10  $\mu\text{mol/L}$ ), an L-type calcium channel blocker, diminished the inhibition of colonic motility by gingerol. Furthermore, gingerol suppressed  $I_{Ba}$  in a dose-dependent manner. Gingerol treatment of colonic longitudinal myocytes of rats resulted in the activation curve being shifted to the right, while the inactivation curve did not change.

Ginger has many uses in many of the world's medi-



**Figure 5** Steady state activation and the steady state inactivation curves. A: Steady state activation for the cells exposed to 6-gingerol, peak conductance was determined from the peak inward currents, corrected for the change in driving force at each of the test potentials and normalized to 1. Driving force was obtained from the difference between the test potential and the observed reversal potential; B: Steady state inactivation relationship. Peak currents were obtained using a two-pulse protocol (3.75 s of prepulse potential from -100 to +40 mV) followed by a 7-ms interpulse interval at -60 mV, and the membrane potential was raised to a test potential of 0 mV for 1 s. The difference between peak current and late current present before and at the end of the test pulse was normalized to 1 and plotted against the prepulse potential.

cinal systems<sup>[1,12,13]</sup>. More commonly, ginger has been traditionally used in disorders of the gastrointestinal tract, as a stomachic, laxative, sialagogue, antiemetic and anti-dyspeptic agent, gastric emptying enhancer and appetizer, and as an antidiarrheal and anti-colic agent<sup>[14]</sup>. Gingerol, which is not a natural component of ginger, is a reduced analogue of gingerone. Most previous studies of gingerol have focused on its anti-cancer, anti-oxidant and anti-inflammatory properties<sup>[1]</sup>. Nigam *et al.*<sup>[15]</sup> reported that the anti-cancer properties of 6-gingerol are mediated by its induction of apoptosis. A previous study indicated that 6-gingerol significantly reduced the DNA strand breaks and micronuclei formation caused by patulin (PAT). Moreover, 6-gingerol effectively suppressed PAT-induced intracellular ROS formation and decreased 8-OHdG level. GSH depletion induced by PAT in HepG2 cells was also attenuated by 6-gingerol pretreatment. These findings suggest that 6-gingerol has a strong protective ability against the genotoxicity caused by PAT and that the antioxidant activity of 6-gingerol may play an important role in attenuating the genotoxicity

of PAT<sup>[16]</sup>. Nonn *et al.*<sup>[17]</sup> reported that 6-gingerol can up-regulate MKP5 and decrease cytokine-induced p38-dependent pro-inflammatory changes.

Recent studies have examined the effect of a component of ginger on diarrhea. It has been demonstrated that zingerone inhibits enterotoxin-induced fluid secretion in the ileum in mice<sup>[18]</sup>. Because excessive fluid secretion by the gastrointestinal tract causes diarrhea, zingerone is likely the active constituent of ginger that is responsible for its antidiarrheal activity. In addition to excessive secretion, abnormal facilitation of gastrointestinal motility is another cause of diarrhea. It has been reported that ginger also has suppressive effects on gut motility. Crude ginger extract inhibits rat ileal motility *via* the inhibition of enteric neural excitatory transmission and smooth muscle mechanical activity *in vitro*<sup>[19]</sup>. Ghayur and Gilani reported inhibitory effects of ginger crude extract on high K<sup>+</sup>-induced contractions in isolated guinea pig colons<sup>[14]</sup>. Furthermore, herbal medicines that include ginger extracts inhibit colonic motility in rats<sup>[10,20]</sup>.

In order to investigate the effect of 6-gingerol on colonic motility and the role of L-type calcium channel in the process, in the present study, we observed the effect of 6-gingerol on spontaneous contraction of colonic longitudinal smooth muscle at different concentrations. The results indicated that spontaneous contraction was significantly inhibited by gingerol. It is in agreement with that of David Banji<sup>[21]</sup>. Furthermore, 6-gingerol obviously inhibited spontaneous contraction in a dose dependent manner. The inhibition percentage was not significantly different between the 75 μmol/L and 100 μmol/L gingerol treatments, indicating that the gingerol concentration of 100 μmol/L is near to its highest effective dose. As we know, there is a close relationship between calcium and muscle contraction. We therefore utilized nifedipine (10 μmol/L), an L-type calcium channel blocker. At a gingerol concentration of 75 μmol/L, after administering nifedipine, the percentage of gingerol-induced inhibition was diminished from 77.1% ± 4.2% to 42.6% ± 3.6%. This indicates that gingerol inhibited spontaneous contraction by inhibiting calcium influx *via* L-type calcium channels, at least in part. This was also shown at a cellular level. These results indicate that the calcium influx *via* L-type calcium channels was diminished by gingerol to inhibit the spontaneous contraction of the colon in rats. Townsend *et al.*<sup>[22]</sup> reported that 6-gingerol prevented Ca<sup>2+</sup> influx through L-type Ca<sup>2+</sup> channels to promote airway smooth muscle relaxation. Furthermore, pretreatment with 20 mmol/L ruthenium red (a ryanodine receptor antagonist) significantly diminished the initial increase of calcium caused by 6-gingerol, suggesting a mechanism of action of 6-gingerol that involves intracellular calcium store depletion. However, we do not know whether intracellular calcium stores participate in the 6-gingerol-induced inhibition of colonic contraction in rats.

Taken together, these findings indicate that 6-gingerol inhibits spontaneous contraction by preventing Ca<sup>2+</sup> influx through L-type calcium channels. Future studies will investigate if intracellular calcium stores participate in this process.

## COMMENTS

### Background

Ginger, an herbal medicine, has been traditionally used to treat various kinds of diseases including gastrointestinal symptoms. Gingerol, a non-pungent analogue of zingerone, which is an active constituent of ginger, can effect on diarrhea *via* inhibiting colonic motility. However, the mechanism of gingerol to inhibit colonic motility is not clear.

### Research frontiers

Gingerol has been reported to possess a variety of biological properties including anti-cancer, anti-oxidant, anti-inflammation, anti-aggregation, antifungal and anti-diarrhea. But the molecular mechanisms underlying the effects of gingerol on gene expression, the signaling pathway and effectual protein involved are required to elucidate.

### Innovations and breakthroughs

Recent reports have highlighted that gingerol will be useful as an oral or suppository medicine for treating diarrhea and other gastrointestinal disorders. Abnormal facilitation of gastrointestinal motility and excessive fluid secretion of the gastrointestinal tract cause diarrhea. There are many ion channels and second messengers involved in this process. However, there is no report in which the effect of gingerol on L-type calcium channel current is described. The purpose of the present study is to clarify the effect of gingerol on colonic motility and the role of L-type calcium channel current in the process.

### Applications

By understanding the effect of gingerol on colonic motility and the role of L-type calcium channel current in the process, this study may help us to understand the mechanism of gingerol to treat diarrhea.

### Terminology

The L-type calcium channel (also known as the dihydropyridine channel, or DHP channel) is part of the high-voltage activated family of voltage-dependent calcium channel. "L" stands for long-lasting referring to the length of activation. This channel has four subunits (Cav1.1, Cav1.2, Cav1.3, and Cav1.4).

### Peer-review

This is a good, solid study with some flaws in data presentation. Part of the discussion, which should refer to newly obtained data, repeats paragraphs from the results section.

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