Effects of Ginger Constituents on the Gastrointestinal Tract: Role of Cholinergic M_3 and Serotonergic 5-HT_3 and 5-HT_4 Receptors

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Key words
- ginger
- *Zingiber officinale* Roscoe
- Zingiberaceae
- gastrointestinal diseases
- cholinergic M_3 receptors
- 5-HT_3 receptors
- 5-HT_4 receptors

Abstract

The herbal drug ginger (*Zingiber officinale* Roscoe) may be effective for treating nausea, vomiting, and gastric hypomotility. In these conditions, cholinergic M_3 receptors and serotonergic 5-HT_3 and 5-HT_4 receptors are involved. The major chemical constituents of ginger are [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol. We studied the interaction of [6]-gingerol, [8]-gingerol, [10]-gingerol (racemates), and [6]-shogaol with guinea pig M_3 receptors, guinea pig 5-HT_3 receptors, and rat 5-HT_4 receptors. In whole segments of guinea pig ileum (bioassay for contractile M_3 receptors), [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol slightly but significantly depressed the maximal carbachol response at an antagonist concentration of 10 µM. In the guinea pig myenteric plexus preparation (bioassay for contractile 5-HT_3 receptors), 5-HT maximal responses were depressed by [10]-gingerol from 93 ± 3% to 65 ± 6% at an antagonist concentration of 3 µM and to 48 ± 3% at an antagonist concentration of 5 µM following desensitization of 5-HT_4 receptors and blockade of 5-HT_1 and 5-HT_2 receptors. [6]-Shogaol (3 µM) induced depression to 61 ± 3%. In rat esophageal tunica muscularis mucosae (bioassay for relaxant 5-HT_4 receptors), [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol (2–6.3 µM) showed no agonist effects. The maximal 5-HT response remained unaffected in the presence of the compounds. It is concluded that the efficiency of ginger in reducing nausea and vomiting may be based on a weak inhibitory effect of gingerols and shogaols at M_3 and 5-HT_3 receptors. 5-HT_4 receptors, which play a role in gastroduodenal motility, appear not to be involved in the action of these compounds.

Introduction

In traditional medicine the powdered rhizome of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has been used for a long time to alleviate the symptoms of gastrointestinal diseases [1–3]. Clinical studies have shown that ginger is effective in reducing motion sickness, postoperative nausea and vomiting, hyperemesis gravidarum, and gastric hypomotility [4–7]. It has been hypothesized that the pharmacological activity of ginger lies in its pungent principles (gingerols and shogaols) and volatile oils (sesquiterpenes and monoterpenes) [8]. The major chemical constituents of the nonvolatile fraction of ginger are the arylalkanes [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol [3].

Attempts were made to characterize the receptor(s) that might be responsible for the therapeutic benefit of ginger on gastrointestinal function. The mechanism of action of ginger is thought to lie in the ability of its active components to affect serotonin (5-HT) and muscarinic receptors in the gastrointestinal tract [9–11]. It has been shown that ginger possesses antiemetic properties against chemotherapy-induced vomiting in laboratory animals [12–14] as well as in humans [15]. The antiemetic effect of ginger was attributed to an antagonist interaction with 5-HT_3 receptors [14]. Interestingly, a contribution of the volatile oil to the 5-HT_3 receptor-mediated antiemetic effect of ginger has recently been suggested [16]. However, ginger was less effective in reducing cisplatin-induced emesis than the selective 5-HT_3 receptor antagonist granisetron [14]. Furthermore, ginger failed to prevent apomorphine-induced emesis, ruling out an involvement of dopamine receptors [14]. In addition, it has been suggested that the antiemetic effect of ginger is associated with an effect on gastric emptying; ginger and its active constituents [6]-gingerol, [8]-gingerol, [10]-

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gingerol, and [6]-shogaol have been reported to enhance gastric emptying of a charcoal meal in mice [17]. This finding is in line with the ability of ginger extracts to reverse cisplatin-induced delay in gastric emptying in rats [18]. The effect of ginger on gastric emptying was similar to that caused by metoclopramide, a 5-HT_4 receptor agonist with antagonist properties at 5-HT_3 receptors, and by ondansetron, a selective 5-HT_3 receptor antagonist [17,18]. Important evidence for the participation of 5-HT_4 receptors in gastric emptying induced by gastrointestinal prokinetics has been provided [19,20]. These findings unequivocally rule out any relevant contribution of 5-HT_3 receptor blockade in the pharmacological action of gastroprokinetics such as metoclopramide [21].

The aim of the present study was to evaluate the effectiveness of [6]-, [8]-, and [10]-gingerol and [6]-shogaol at cholinergic M_3 receptors in whole segments of guinea pig ileum, at serotonergic 5-HT_3 receptors of the longitudinal muscle-myenteric plexus preparation of guinea pig ileum, and at 5-HT_4 receptors of rat esophageal tunica muscularis mucosae. Based on the pharmacological profile of [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol, an antiemetic effect of ginger may be caused by the weak inhibitory properties of these compounds at the M_3 and 5-HT_3 receptors. The prokinetic properties of ginger are not mediated by a specific interaction with 5-HT_4 receptors.

Materials and Methods

Chemicals

[6]-Gingerol, [8]-gingerol, and [10]-gingerol (racemates) were synthesized in-house according to previously described standard procedures [22]. [6]-Shogaol was obtained from [6]-gingerol by dehydration. The purity of the compounds was > 95% (analyzed by HPLC). The following drugs were obtained as gifts: methysergide hydrogen maleate (purity > 99%) and tropisetron hydrochloride (purity > 99%) (Novartis). The following compounds were purchased: atropine sulfate (purity > 97%) and cocaine hydrochloride (purity > 98.5%) (Merck); carbachol (purity > 98%), corticosterone (purity > 92%), 5-methoxytryptamine (purity 97%), pargyline hydrochloride (purity > 98%), and SDZ-205557 hydrochloride (purity > 99%) (Sigma-Aldrich); and choline chloride (purity > 99%) and 5-hydroxytryptamine creatinine sulfate (purity > 99%) (Janssen).

Animals

Animal studies were approved by Landesamt für Gesundheit und Soziales Berlin, Germany (ZH 12, T0035/00). All experimental procedures carried out in the present studies followed the guidelines of the Animals (Scientific Procedures) Act 1986. Male Wistar rats (250–300 g) and guinea pigs (250–450 g) were housed in plastic cages in a special temperature-controlled room (22 ± 2 °C, 50% humidity) on a 12:12-h light/dark cycle (light on at 07:00). They were allowed *ad libitum* access to food and water. Guinea pigs were stunned by a blow to the neck and bled. Rats were killed by decapitation following asphyxiation with CO_2.

Cholinergic M_3 receptor assay (guinea pig ileum)

Whole segments of guinea pig ileum (1.5 cm in length) were dissected and suspended in a water-jacketed 20-mL organ bath that contained Tyrode solution of the following composition (mM): NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.0, NaH_2PO_4 0.4, $NaHCO_3$ 11.0, and glucose 5.6. The solution was gassed with 95% O_2/5% CO_2 and warmed to a constant temperature of 37 °C (pH 7.4). One end of the segment was fixed on the bottom of the organ bath and the other was attached to an isotonic lever for continuous measurement of length changes. Preload at the beginning of the experiment was 7.5 mN. After a stabilization period of 20 min, the segments were stimulated three times with carbachol (1 µM) for a period of 45 min until the magnitude of the contractile response became constant. Four cumulative concentration-response curves were constructed at intervals of 15–20 min: the first curve to carbachol and the second through fourth curves to carbachol in the presence of antagonist or vehicle. Antagonists were incubated for 10 min. Previous studies by this group showed that successive concentration-response curves to carbachol in the absence of antagonist (control curves) were highly reproducible in guinea pig ileum (no differences in pEC_{50} or E_{max} values). Contractile responses were expressed as a percentage value of the maximal response to carbachol in the first curve.

Serotonergic 5-HT_3 receptor assay (guinea pig myenteric plexus)

Strips of longitudinal muscle with adhering myenteric plexus from guinea pig ileum (1.5 cm in length) were prepared as previously described [23]. The strips were placed for the measurement of isometric changes in tension in 20-mL organ baths filled with Tyrode solution that additionally contained choline (1 µM) for *de novo* synthesis of acetylcholine, 5-methoxytryptamine (10 µM) for desensitization of 5-HT_4 receptors, and methysergide (1 µM) for blockade of 5-HT_1 and 5-HT_2 receptors [24]. The solution was continuously gassed with 95% O_2/5% CO_2 and warmed to a constant temperature of 37 °C (pH 7.4). The resting tension was adjusted to 7.5 mN at the beginning of each experiment. After a stabilization period of 30 min, the tissues were stimulated three times with 5-HT (3 µM) for a period of 60 min. Two noncumulative concentration-response curves were constructed at an interval of 60 min on each tissue by adding increasing concentrations of 5-HT (1–30 µM) to the organ bath. Each concentration was left in contact with the tissue for 15–30 s followed by washout with Tyrode solution (100 mL). The next higher concentration of 5-HT was administered 15 min later. Antagonists or vehicle were added 30 min before the second concentration-response curve and were retained in the bath fluid during construction of the second curve. Contractile responses were expressed as a percentage value of the maximal response to 5-HT in the first curve. Two noncumulative concentration-response curves to 5-HT on the same tissue (control curves) were highly reproducible, with the pEC_{50} of the first curve (5.57 ± 0.02) being practically identical to that of the second curve (5.50 ± 0.06; n = 24). The E_{max} of the second 5-HT curve was 97 ± 1% relative to the E_{max} of the first curve.

Serotonergic 5-HT_4 receptor assay (rat esophageal tunica muscularis mucosae)

The entire rat esophagus was excised and the outer striated muscle layer of the tunica propria was removed by microdissection, leaving behind the inner smooth muscle tube of the tunica muscularis mucosae [25]. The muscle tube was divided into a proximal (cervical), middle (thoracic), and distal (abdominal) segment. From each segment, 2–3 strips were cut longitudinally and placed in Tyrode solution (pH 7.4, 37 °C) for measurement of isometric changes in tension. The Tyrode solution additionally contained methysergide (1 µM) to inhibit 5-HT_1 and 5-HT_2 receptors and cocaine (30 µM) and corticosterone (30 µM) to inhibit

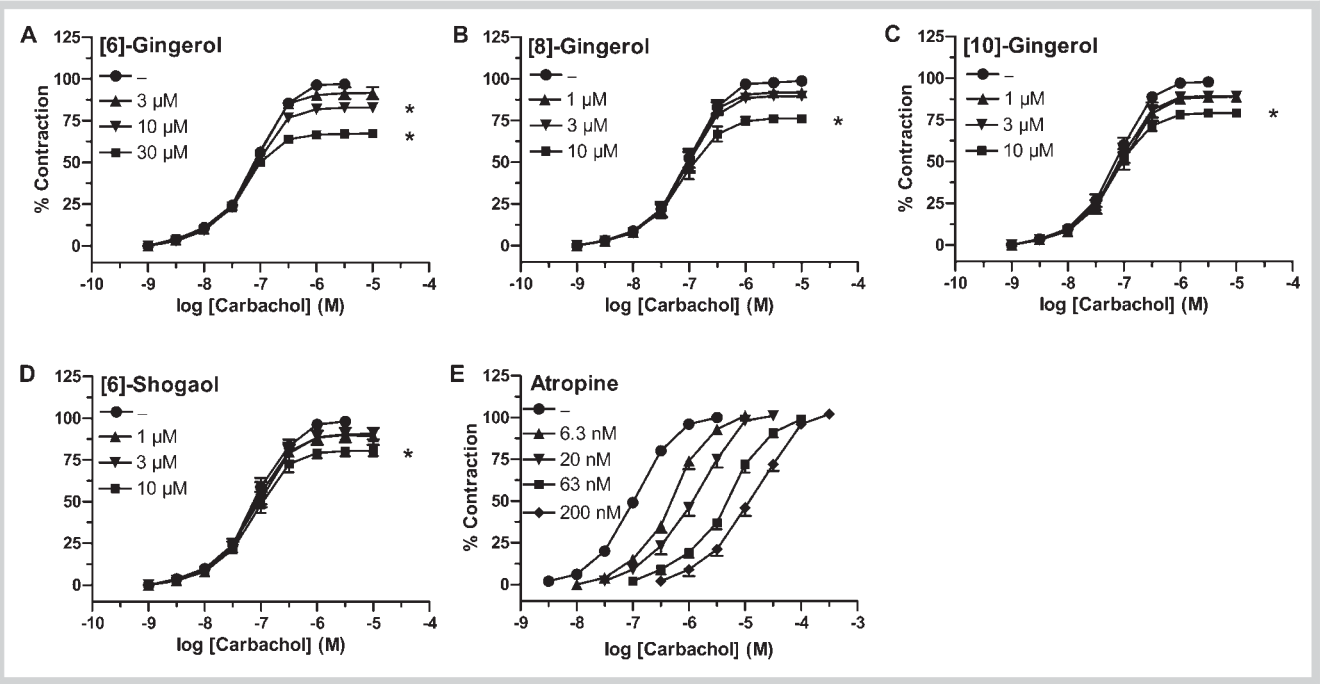

Fig. 1 Inhibition of carbachol-induced contraction by [6]-gingerol (**A**), [8]-gingerol (**B**), [10]-gingerol (**C**), [6]-shogaol (**D**), and atropine (M_3 receptor antagonist; **E**) in guinea pig ileum. Shown are cumulative concentration-response curves to carbachol in the absence and presence of antagonist. Data are the mean ± SEM from 4–6 animals; * $p < 0.05$.

neuronal and cellular uptake of 5-HT. The resting tension was adjusted to 1.5 mN at the beginning of each experiment. During a stabilization period of 30 min, the tissues were exposed to pargyline (100 µM) to inhibit monoamine oxidases. The tissues were allowed to equilibrate for a further 30 min. After the stabilization and equilibration period, during which the tissues were washed with Tyrode solution (200 mL) every 15 min, the tissues were contracted with a submaximal concentration of carbachol (3 µM) until the magnitude of the contractile response became constant (usually after 40 min). The relaxant response to 5-HT or arylalkanes was studied by constructing a cumulative concentration-response curve. For determination of antagonist affinity, a second concentration-response curve to 5-HT was performed following a further carbachol-induced (3 µM) contraction. Antagonists or vehicle were incubated for 60 min. Effects were expressed as a percentage value of the maximal relaxation evoked by 5-HT in the first curve. Two cumulative concentration-response curves to 5-HT on the same tissue (control curves) were highly reproducible, with the pEC_{50} of the first curve (8.02 ± 0.07) being practically identical to that of the second curve (8.00 ± 0.06; $n = 15$). The E_{max} of the second 5-HT curve was 100 ± 2% relative to the E_{max} of the first curve.

Data presentation and statistical evaluation

Data are presented as the mean ± SEM for n animals. Agonist potencies and maximal responses are expressed as pEC_{50} values (negative logarithm of the molar concentration of agonist producing 50% of the maximal response) and E_{max} values, respectively. In cases where an antagonist caused a parallel shift of an agonist curve, a Schild plot of log (concentration ratio – 1) versus log (antagonist concentration) was constructed, and a pA_2 was calculated from the x-intercept of this plot. A slope of the Schild plot of 1 indicated competitive antagonism.

Where appropriate, differences between means were determined by Student's t-test (two-tailed), after checking the homogeneity of the variances. P values of less than 0.05 were considered to indicate a significant difference between the responses being compared.

Results

The effects of [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol on cholinergic M_3 receptors are shown in **Fig. 1 A–D**. In contrast to the effect of the reference antagonist atropine, which behaved as a competitive M_3 receptor antagonist (pA_2 = 8.81 ± 0.03, slope of the Schild plot = 1.05 ± 0.03; **Fig. 1 E**), [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol (1–30 µM) failed to evoke a rightward shift of the concentration-response curve to carbachol. However, the E_{max} values of carbachol were significantly depressed at an antagonist concentration of 10 µM. Thus, ginger ingredients affected cholinergic M_3 receptors only at high concentrations and in a noncompetitive manner. [6]-Gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol did not evoke a contractile response via stimulation of cholinergic M_3 receptors.

The effects of [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol on serotonergic $5\text{-}HT_3$ receptors are shown in **Fig. 2 A–D**. The $5\text{-}HT_3$ receptor-mediated contraction of guinea pig ileum by 5-HT is an indirect response that is based on the release of acetylcholine from intramural cholinergic nerves in the myenteric plexus followed by activation of cholinergic M_3 receptors on the longitudinal smooth muscle cell. At concentrations not interfering with M_3 receptors (1–6.3 µM), there was no difference in the pEC_{50} values of 5-HT in the absence or presence of [6]-shogaol, [6]-gingerol, [8]-gingerol, and [10]-gingerol. However, E_{max} values were significantly depressed in the presence of

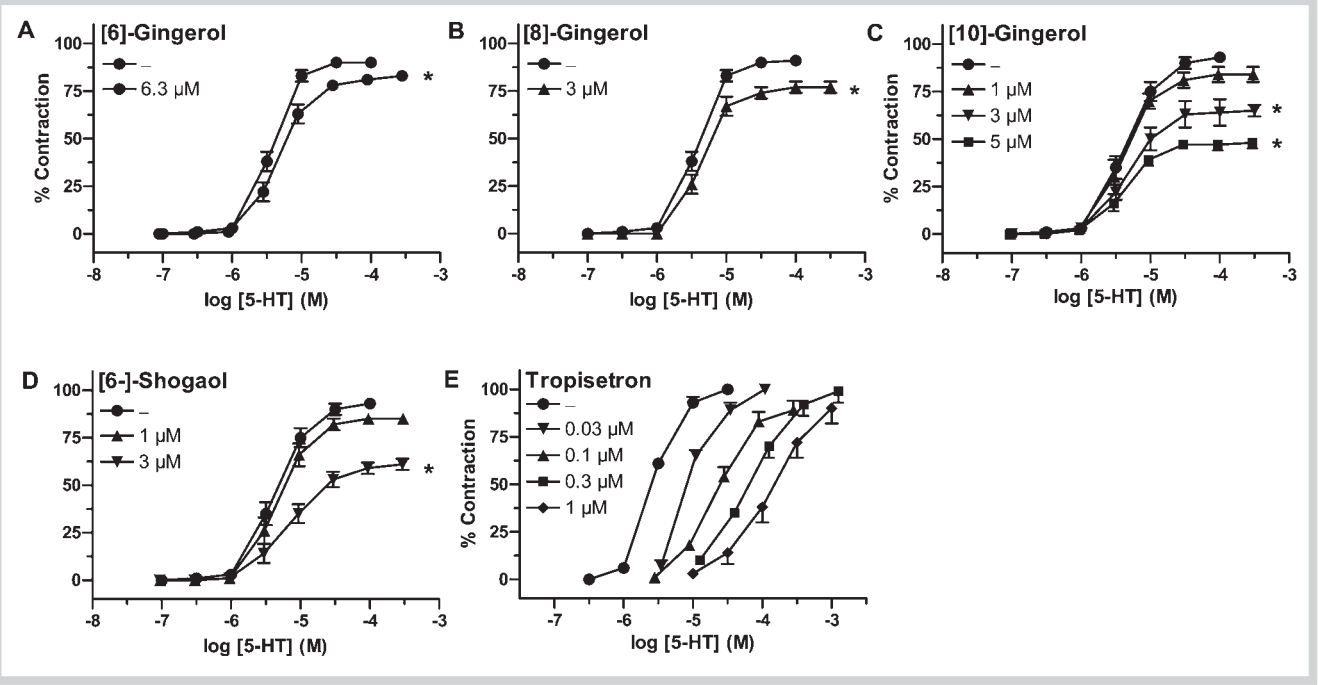

Fig. 2 Inhibition of 5-HT-induced contraction by [6]-gingerol (**A**), [8]-gingerol (**B**), [10]-gingerol (**C**), [6]-shogaol (**D**), and tropisetron (selective 5-HT_3 receptor antagonist; **E**) in the longitudinal muscle-myenteric plexus preparation of guinea pig ileum following desensitization of 5-HT_4 receptors and blockade of 5-HT_1 and 5-HT_2 receptors (see Materials and Methods). Shown are noncumulative concentration-response curves to 5-HT (second curves) in the absence and presence of antagonist. Data are the mean ± SEM from 4–6 animals. * $p < 0.05$.

the compounds. Most potent was [10]-gingerol, which concentration-dependently decreased the maximal 5-HT response from 93 ± 3% (control) to 65 ± 6% at an antagonist concentration of 3 µM and to 48 ± 3% at an antagonist concentration of 5 µM. [6]-Shogaol (3 µM) showed similar antagonist effects by decreasing the maximal 5-HT response to 61 ± 3%. Thus, gingerols and [6]-shogaol affected 5-HT_3 receptor-mediated ileal contractions in a noncompetitive manner. [6]-Gingerol, [8]-gingerol [10]-gingerol, and [6]-shogaol did not induce a contractile effect via stimulation of 5-HT_3 receptors. Tropisetron, which was used as a reference antagonist, behaved as a competitive 5-HT_3 receptor antagonist ($pA_2 = 7.84 \pm 0.03$, slope of the Schild plot = 1.00 ± 0.04; **Fig. 2E**). The effects of [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol on serotonergic 5-HT_4 receptors are shown in **Fig. 3A–D**. The compounds failed to induce a relaxant response via stimulation of 5-HT_4 receptors of rat esophageal tunica muscularis mucosae. In the presence of the compounds (2–6.3 µM), there was no rightward shift of the concentration-response curve to 5-HT. SDZ-205557, which was used as a reference antagonist, showed competitive 5-HT_4 receptor antagonist properties ($pA_2 = 7.34 \pm 0.05$, slope of the Schild plot = 0.95 ± 0.06; **Fig. 3E**).

Discussion

It is well established that 5-HT_3 receptor antagonists are efficient in the treatment of emesis induced by cancer chemotherapy and radiotherapy and in the prevention and treatment of postoperative nausea and vomiting [26]. From the present study, it is possible that the efficiency of the herbal drug ginger against chemotherapy-induced emesis [14,15] and postoperative nausea and vomiting [5], at least at high dosage, may be due to an interaction with 5-HT_3 receptors. In contrast to selective 5-HT_3 receptor antagonists such as tropisetron, which has been shown to competitively block 5-HT_3 receptor-mediated contractions in guinea pig ileum (**Fig. 2E**), [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol failed to produce a rightward shift of the concentration-response curve to 5-HT (**Fig. 2A–D**). A significant attenuation of the 5-HT maximal response in the presence of [8]-gingerol, [10]-gingerol, and [6]-shogaol was detected at an antagonist concentration of 3 µM (**Fig. 2A–D**). The noncompetitive inhibitory effects of the compounds may be mediated by binding to a modulatory site distinct from that of 5-HT. Our results are in accordance with recently published studies that demonstrated a weak inhibitory effect of ginger constituents via a noncompetitive blockade of 5-HT_3 receptors [11,27]. However, it should be mentioned that arguments against the effectiveness of ginger in reducing the incidence of postoperative nausea and vomiting have also been presented [28]. Further studies are needed to substantiate the antiemetic properties of ginger via a blockade of 5-HT_3 receptors.

A current therapeutic application for ginger is motion sickness, although the effectiveness of the herbal drug for this indication seems to be controversial [4,29]. In general, anticholinergic agents such as scopolamine are useful in the prevention and treatment of motion sickness. Due to the inability of ondansetron to be effective against motion sickness in humans, it has been concluded that 5-HT_3 receptors are not involved in the neural pathways that bring about motion sickness [30]. This finding suggests that any potential activity of ginger against motion sickness would be independent from the 5-HT_3 receptor blockade and might instead be based on a blockade of muscarinic receptors. Our study showed that ginger ingredients slightly but significantly affected cholinergic M_3 receptors only at high concentra-

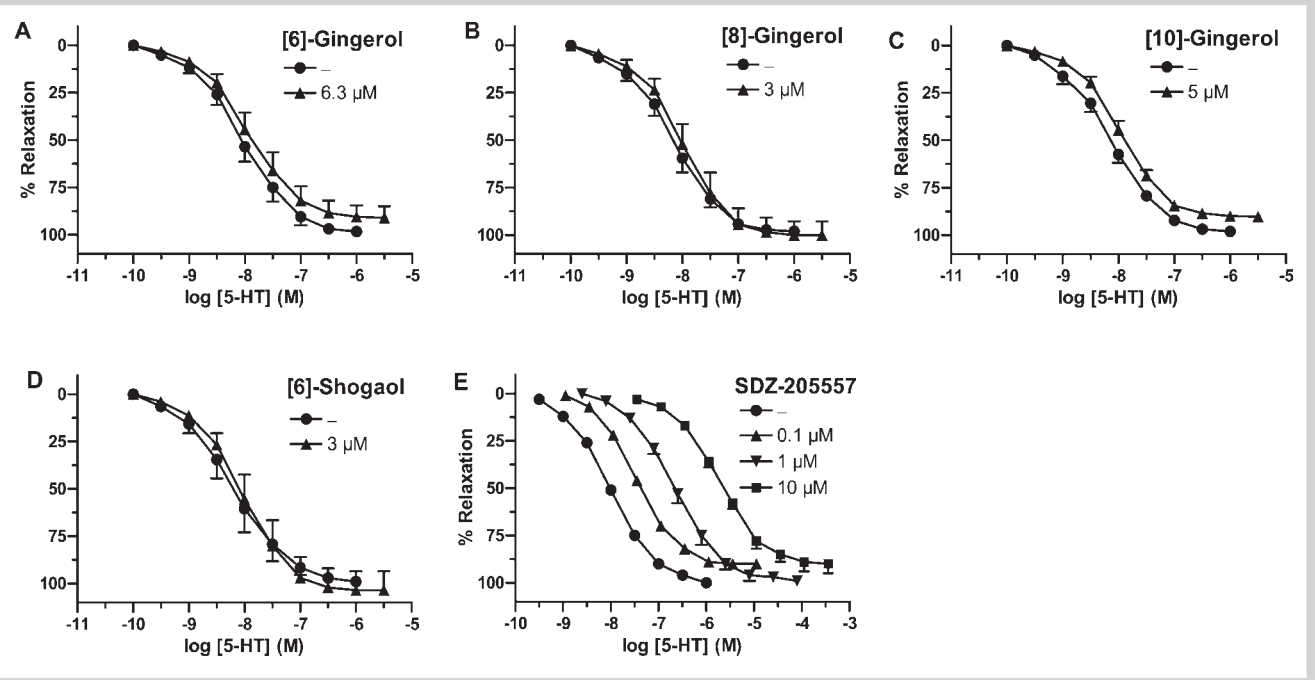

Fig. 3 Effects of [6]-gingerol (**A**), [8]-gingerol (**B**), [10]-gingerol (**C**), [6]-shogaol (**D**), and SDZ-205557(selective 5-HT_4 receptor antagonist; **E**) on 5-HT-induced relaxation in rat esophageal tunica muscularis mucosae. Shown are cumulative concentration-response curves to 5-HT (second curves) in the absence and presence of antagonist. Data are the mean ± SEM from 4 animals.

tions. Our results are in accordance with the results of other studies [10,11]. Surprisingly, it was recently shown that a ginger extract had an agonistic effect on cholinergic M_3 receptors [31]. This observation is in contrast to our results obtained with [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol.

A further aspect which is uncertain is the improvement of gastric emptying induced by ginger. Micklefield et al. [7] reported that oral ginger improved gastroduodenal motility, while Phillips et al. [32] found that ginger had no effect on gastric emptying. Efforts were made to elucidate the mode of action underlying the potential prokinetic effect of ginger. It was suggested that the enhancement of gastrointestinal motility by ginger is mediated by a blockade of 5-HT_3 receptors, since the effect was similar to that caused by metoclopramide and ondansetron [17,18]. It should be emphasized, however, that the gastrointestinal prokinetic activity of metoclopramide is based on the agonist properties of this drug at 5-HT_4 receptors [33]. 5-HT_4 receptor activation facilitates acetylcholine release from cholinergic neurons, thereby triggering the peristaltic reflex [34]. The present study on ginger rules out any interaction of ginger constituents with 5-HT_4 receptors, which are the responsible targets for serotonergic prokinetic agents. Our study shows that [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol failed to possess agonist activity at 5-HT_4 receptors. Therefore, a role for ginger in stimulating gastrointestinal motility via 5-HT_4 receptors is unlikely. Interestingly, it was recently demonstrated that ginger failed to improve delayed gastrointestinal transit in rat postoperative ileus, a process in which the 5-HT_4 receptor is partly involved [35].

In conclusion, our data support the possibility that the herbal drug ginger may be beneficial in reducing nausea and vomiting due to the weak inhibition of cholinergic M_3 receptors and serotonergic 5-HT_3 receptors by gingerols and shogaols. However, a prokinetic effect of gingerols and shogaols via stimulation of 5-HT_4 receptors can be excluded. Admittedly, a prokinetic effect of ginger might be mediated by other pathways, such as the inhibition of L-type Ca^{2+} channels [36]. [6]-Gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol have in common that they inhibited agonist responses to carbachol and 5-HT in a noncompetitive manner (**Figs. 1A–D** and **2A–D**) in contrast to the reference antagonists (atropine and tropisetron), which showed competitive antagonism (**Figs. 1E** and **2E**). The present study has certain limitations. Most notably, we tested the racemates of [6]-gingerol, [8]-gingerol, and [10]-gingerol instead of the naturally occurring enantiomer. It would be particularly interesting to clarify whether the stereochemistry of natural occurring gingerols plays an essential role in the antiemetic activity of ginger. This may not be the case, since the achiral component of ginger, [6]-shogaol, was at least equally potent to gingerols in inhibiting 5-HT_3 and M_3 receptor function in this and in other studies [9,11,27]. In addition, our studies were restricted to the pharmacological profile of [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol. However, other nonvolatile constituents of ginger (e.g., diacetyl-[6]-gingerdiol and [6]-dehydrogingerdione) and volatile oil constituents have also been demonstrated to possess 5-HT_3 receptor-blocking properties [16,27]. Nonetheless, the current data support the finding that ginger is useful against nausea and vomiting [37].

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