Gastrointestinal Motility Enhancing Effect of Ginger and Its Active Constituents

Johji YAMAHARA,* Qirong HUANG, Yuhao LI, Lin XU and Hajime FUJIMURA

Kyoto Pharmaceutical University, 5 Misasagi Nakauchi-cho, Yamashina-ku, Kyoto 607, Japan. *Received July 20, 1989*

The effect of ginger root (Zingiberis Rhizoma) on gastrointestinal motility was examined based on its ability to enhance charcoal meal transport in mice. Oral administrations of the acetone extract of ginger (which contains volatile oils and bitter substances) at 75 mg/kg, [6]-shogaol at 2.5 mg/kg, or a [6]-, [8]- or [10]-gingerol at 5 mg/kg enhanced the transport of a charcoal meal. The effects of these substances were similar to or slightly weaker than those of metoclopramide and donperidone.

Keywords ginger; gastrointestinal motility; [6]-shogaol; gingerol

There are many reports on the pharmacological effects of ginger,[1] which is a stomachic and a spice, but there are few reports describing the stomachic property of ginger. We have already reported on the bile secretion-enhancing action and antiulcer effect of ginger. In order to support the possible use of ginger to treat abdominal pain and as an antivomiting agent, we have also examined the anti 5-hydroxytryptamine (5-HT) effect in isolated smooth muscles[2] and antivomiting action in suncus.[3] Based on a recent report[4,5] that not only antagonists of dopamine but also 5-HT antagonists, especially 5-HT_3 antagonists, enhance gastrointestinal motility, the effect of ginger on gastrointestinal motility was examined with the aim of obtaining evidence substantiating the stomachic effect of ginger. The results in the present study indicated that [6]-shogaol, [6]-, [8]- and [10]-gingerol enhanced gastrointestinal motility.

Experimental Materials and Procedure

Experimental Materials Ginger (*Zingiber officinale* ROSCOE, Zingiberaceae), which was of Japanese Pharmacopeial standard, was obtained from the Osaka market and was cut into 5 mm blocks and then powdered. Acetone extract of ginger was obtained as follows. Five volumes of acetone was added to ginger and filtered. This was repeated 3 times. The filtered solution was concentrated to dryness under reduced pressure at below 40 °C. The yield of the extract was 3.4% from the ginger powder.

The acetone extract was fractionated into 4 fractions by column chromatography on Silica gel 60 (70—230 mesh, Merck) with hexane–hexane : ethyl acetate(hexane only 5 : 1—5 : 2). The yields of fr. 1, fr. 2, fr. 3 and fr. 4 were 14%, 12%, 50% and 15%, respectively from the extract. Fraction 2 and fr. 3 were purified repeatedly by silica gel column chromatography, and final purification was achieved by a reverse-phase silica gel (Silica gel 60 silanized, Merck) medium-pressure column chromatography (Minimicro pump KHD-W-294, Kyowa Seimitsu Co., Ltd., Tokyo, Japan) with 55% and 60% methanol. [6]-Shogaol (mol wt. 276.38) was obtained from fr. 2 in about 19.0% yield. Fraction 3 was further fractionated and [6]-gingerol (mol wt. 294.18) was obtained from fr. 3-1 in 64.8% yield, [8]-gingerol (mol wt. 322.21) from fr. 3-2 in 7.53% yield and [10]-gingerol (mol wt. 305.25) from fr. 3-3 in 33.0% yield. These compounds were identified on the basis of their mass spectra (MS), and nuclear magnetic resonance (NMR) and infrared (IR) (absorption) spectra. Concentrations of drugs were adjusted so that the volume of administration was 0.1 ml/10 g of body weight. Atropine sulfate (Merck), metoclopramide (Sigma, mol wt. 299.81) and donperidone (Kyowa Hakko Kogyo, mol wt. 425.92) were used as reference drugs.

Experimental Procedure Male ddY mice (Oriental Bio Service) weighing 20—23 g (40—41 d old) were used (8—11 mice in a group). Mice were fasted for 18 h (water was freely available) prior to experiments, and test drugs suspended in 2% acacia were orally administered. Fifteen minutes thereafter, 0.2 ml of charcoal meal (5% charcoal suspended in 1% carboxymethyl cellulose) was orally administered. Thirty minutes thereafter, the mice were killed by cervical dislocation and the abdomen were immediately opened to excise the whole small intestine (the pylorus region to about the cecum). The length of the small intestine (the pylorus region to the ileocecal region) and the distance between the pylorus region and the front of the charcoal meal were measured. For statistical analysis, the ratio of the distance the charcoal meal had moved to the whole length of the small intestine (charcoal transport ratio, %) was obtained and differences between control groups and drug groups were analyzed by the use of

TABLE I. Effects of Zingiberis Rhizoma Acetone Extract, Metoclopramide and Atropine on Gastrointestinal Motility as Measured with 5% Activated Charcoal in Male ddY Mice

Sample	Dose mg/kg, *p.o.*	No. of animals	Intestine transport: 5% activated charcoal transport ratio (%)[a]	Intestine transport: Advancement change (%)
Vehicle (2% acacia)	—	10	48.6±4.5	—
Zingiberis Rhizoma Acetone extract	75	10	70.0±4.5[b]	43.9
	150	10	73.7±3.3[b]	51.6
Vehicle (2% acacia)	—	10	40.6±1.8	—
Metoclopramide	10	8	60.2±4.9[b]	48.1
Vehicle (2% acacia)	—	10	45.7±3.7	—
Donperidone	10	10	52.0±3.5	13.7
Atropine	3	9	29.2±1.9[b]	−36.2

Test drugs and Vehicle were given *p.o.* 15 min before the oral administration of 5% activated charcoal, and 30 min later, the animals were killed by cervical dislocation. *a*) The distance that the charcoal had travelled from the pylorus was expressed as a percentage of the length of the small intestine; each value represents the mean±S.E. *b*) $p<0.01$: significant difference from vehicle control.

TABLE II. Effects of Zingiberis Rhizoma Acetone Extract, Fraction, on Gastrointestinal Motility as Measured with 5% Activated Charcoal in Male ddY Mice

Sample	Dose mg/kg, *p.o.*	No. of animals	Intestine transport: 5% activated charcoal transport ratio (%)[a]	Intestine transport: Advancement change (%)
Vehicle (2% acacia)	—	10	45.7±3.7	—
Zingiberis Rhizoma Acetone extract	150	10	79.9±3.4[b]	74.8
Fr. 1	75	10	73.5±6.3[b]	60.8
Fr. 2	150	9	77.4±4.4[b]	69.2
Fr. 3	120	8	69.5±4.7[b]	51.8
Fr. 4	30	9	67.8±4.9[b]	48.1
Vehicle (2% acacia)	—	10	48.9±3.9	—
Metoclopramide	5	8	68.9±5.2[b]	40.8

Tested drugs and vehicle were given *p.o.* 15 min before the oral administration of 5% activated charcoal, and 30 min later, the animals were killed by cervical dislocation. *a*) The distance that the charcoal had travelled from the pylorus was expressed as a percentage of the length of the small intestine; each value represents the mean±S.E. *b*) $p<0.01$: significant difference from vehicle control.

Table III. Effects of [6]-Shogaol, [6]-, [8]-, [10]-Gingerol and Metoclopramide on Gastrointestinal Motility as Measured with 5% Activated Charcoal in Male ddY Mice

Sample	Dose mg/kg, *p.o.*	No. of animals	Intestine transport	
			5% activated charcoal transport ratio (%)[a]	Advancement change (%)
Vehicle (2% acacia)	—	10	48.9±3.9	—
[6]-Shogaol	1	10	57.3±5.0	17.1
	2.5	10	65.4±3.1[c]	33.7
	5	10	68.6±4.6[c]	40.2
Vehicle (2% acacia)	—	10	40.6±1.8	—
[6]-Shogaol	10	11	67.0±3.6[c]	64.8
[6]-Gingerol	10	11	61.8±3.4[c]	52.1
Vehicle (2% acacia)	—	10	48.9±3.9[c]	—
[8]-Gingerol	1	10	50.6±4.5	3.4
	2.5	10	60.0±5.0	22.7
	5	10	62.6±3.9[b]	28.0
Vehicle (2% acacia)	—	10	40.6±1.8	—
[8]-Gingerol	10	11	65.7±5.4[c]	61.7
[10]-Gingerol	10	10	59.2±5.1[c]	45.8
Vehicle (2% acacia)	—	10	48.9±3.9	—
Metoclopramide	5	8	68.9±5.2[c]	40.8

Test drugs and vehicle were given *p.o.* 15 min before the oral administration of 5% activated charcoal, and 30 min later, the animals were killed by cervical dislocation. *a*) The distance that the charcoal had travelled from the pylorus was expressed as a percentage of the length of the small intestine; each value represents the mean±S.E. *b*) $p<0.05$, *c*) $p<0.01$: significant difference from vehicle control.

Student's *t* test.

Experimental Results 1) Effect of Acetone Extract of Ginger: The acetone extract at 75 mg/kg *p.o.* significantly enhanced the charcoal transport as shown in Table I.

2) Effect of Each Fraction of Acetone Extract of Ginger: Each of the fractions at dosages determined on the basis of their respective yield from the acetone extract was significantly effective as shown in Table II. The effects of bitter principles obtained from fr. 2 and fr. 3 were further examined.

3) Effects of [6]-Shogaol, and [6]-, [8]- and [10]-Gingerol: Table III indicates that each of these drugs at 10 mg/kg *p.o.* showed a significant effect, which was slightly weaker than that of metoclopramide.

Discussion

There are many drugs which enhance gastrointestinal motility, such as metoclopramide (a benzamide) and donperidone (a dopamide antagonist).[5] Among natural stomachics, one of the mechanisms of action may be considered to be gastrointestinal motility-enhancing action, but this has been proven in only a few cases. There have been many pharmacological studies of ginger but there is one study[6] indicating the enhancement of intestinal transport of barium sulfate by a 50% methanol extract of ginger and there has been no work done to identify the active constituents. Our previous results indicate that gingerols, the pungent principles in ginger, inhibit the contractions induced by 5-HT in guinea pig ileum[2] more than in isolated blood vessels and gastric smooth muscles, and that gingerols have antivomiting action in suncus[3] thus suggesting anti 5-HT_3 action.

The present findings that [6]-shogaol and [8]-gingerol at low concentrations of 2.5 and 5 mg/kg, respectively, enhanced charcoal transport in mice not only may provide a basis for development of new types of intestinal motility-enhancing drugs but also substantiates the importance of bitter principles as one of the important parameters for quality valuation. Currently, the characteristics of anti-5-HT action of [6]-shogaol, gingerols and other active constituents are being investigated.

References

1) M. Aburada, *J. Traditional Sino-Japanese Medicine*, **8**, 45 (1987).
2) J. Yamahara, Q. R. Huang, M. Iwamoto, G. Kobayashi, H. Matsuda and H. Fujimura, *Phytotherapy Research*, **3**, 70 (1989).
3) J. Yamahara, Q. R. Huang, Y. Naitoh, T. Kitani and H. Fujimura, *J. Ethnopharmacology*, **27**(3), 353 (1989).
4) M. S. Hadiey, F. D. King, B. McRitchie, D. H. Turner and E. A. Watts, *J. Med. Chem.*, **28**, 1843 (1985).
5) F. D. King and G. J. Sanger, "Annual Reports in Medicinal Chemistry," Vol. 23, Academic Press, Inc., California, 1988, p. 201.
6) Y. Kasahara, E. Saito and H. Hikino, *Shoyakugaku Zasshi*, **37**, 73 (1983).