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Pharmacological Studies on Chinese Cinnamon. II.[1] Effects of Cinnamaldehyde on the Cardiovascular and Digestive Systems

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Effects of cinnamaldehyde (CA) on the cardiovascular and digestive systems were examined.

CA produced a hypotensive effect in anesthetized dogs and guinea pigs, which seemed to be due mainly to its peripheral vasodilatation. The vasodilatation induced by CA in dogs lasted and remained over the recovery period of the fall in blood pressure to its original level. A papaverine-like musculotropic activity of CA, which was shown in the isolated ileum from the guinea pig and the mouse, seemed to participate in the vasodilatation. CA exerted an increase in cardiac contractile force and beating rate in the isolated guinea pig heart preparations, that is, isolated atria and perfusing heart. The actions were distinct from those of adrenaline as a lag time was needed for the appearance of positive inotropic and chronotropic effects. The repeated applications of CA, however, decreased such effects and led to a cardiac inhibition. Coronary flow was increased.

CA moderately inhibited both the rat stomach movement and the mouse intestinal propulsion. Gastric erosions produced in stressed mice were protected by oral administration of CA. In rats, CA increased biliary excretion.

Some discussions were made upon the relation between pharmacological effects of CA and therapeutic effects of chinese cinnamon.

Following the previous study[1] of cinnamaldehyde (CA) on the central pharmacological effects, we examined its cardiovascular and digestive effects in the present study. In addition, some discussions were made upon the relation between pharmacological effects of CA and therapeutic effects of chinese cinnamon.

Experimental

Material

CA was suspended in 0.5% sodium carboxymethylcellulose (CMC) saline solution for the application except coronary injection where CA was suspended in the perfusing solution.

Animal

Mongrel dogs of either sex (10—15 kg), male guinea pigs (300—400 g), male Wistar strain rats (200—400 g) and male dd strain mice (18—20 g) were used.

Method

1. Effects on the Cardiovascular System——a) Effects on Blood Pressure, Respiration, Peripheral Blood Flow and Heart Rate: Dogs were anesthetized with 30 mg/kg *i.v.* of sodium pentobarbital. A tracheal tube was inserted, to which a Marey's tambour was attached. Respiration was recorded using a

1) Part I: M. Harada and Y. Ozaki, *Yakugaku Zasshi*, **92**, 135 (1972).

2) Location: *Yayoi-cho, Chiba.*

force displacement transducer (Nihon Kohden, SB-1T) which was connected with the tambour by a thread. A catheter was placed in the femoral artery to record blood pressure using a pressure transducer (Nihon Kohden, MPU-0.5). A probe of an electromagnetic flowmeter (Nihon Kohden, MF-2) was set around another femoral artery to record femoral arterial blood flow. Heart rate was measured by a cardiotachometer (Nihon Kohden, RT-2) triggered from the pulse wave. All parameters were recorded on a polygraph (Nihon Kohden, RM-150). Electrocardiogram was taken *via* lead II (Nihon Kohden, MC-3). The drug was applied either *via* the cephalic vein in the case of systemic administration or *via* the femoral artery for the determination of femoral blood flow. Arterial injection was made in a constant volume (0.1 ml) and a constant speed (3 sec). Guinea pigs were anesthetized with 35 mg/kg *i.v.* of sodium pentobarbital. Blood pressure was recorded *via* the carotid artery by a pressure transducer (Nihon Kohden, MPU-0.5).

b) Effect on the Isolated Guinea Pig Hearts: i) Isolated atria; Isolated atria were suspended in Tyrode solution saturated with O_2 and maintained at 31° according to Magnus' method. Recording of atrial contraction was made either isotonically using a lever on a kymographion or isometrically using a force displacement transducer (Nihon Kohden, SB-1T) on a pen-writing recorder (Nihon Kohden, WI-130). ii) Isolated perfusing hearts; Cardiac contractile force, heart rate and coronary flow were evaluated according to Langendorff's method (Krebs-Hensleit solution, 32°, perfusing pressure 60 mmH_2O). Cardiac force was recorded isometrically in the same manner as described in i). Drugs were administered in a constant volume (0.1 ml) and a constant speed (30 sec) *via* the rubber tube connected to the cardiac cannula.

2. Effects on the Digestive System——a) Effect on the Rat Gastric Secretion: The procedure was done according to Rosenoer and Schild's method.[3] Rats were anesthetized with 1 g/kg *i.p.* of urethane. Phosphate citrate buffer solution adjusted to pH 7.5 was introduced in the stomach under a constant speed of 1 ml/min *via* the fundus and drained out *via* the pylorus. The change of pH value of the perfusate was continuously recorded by a pH recorder (Hitachi-Horiba, M-5). Drugs were given *i.v.*

b) Effect on the Rat Stomach Movement: Rats were anesthetized as described above. A balloon attached to a polyethylene tube was filled with water and placed in the glandular portion of the stomach through the forestomach. The opposite terminal of the tube was connected to one end of a glass U tube. A float was put on the surface of water in the another end of the tube so that a change of stomach pressure could be recorded on a kymograph. Drugs were administered *i.v.*

c) Effect on the Stress-induced Gastric Erosion in Mice: The examination was carried out according to the method[4] developed by us. Mice fasted overnight were restrained in appropriate cages and immersed in 25° water for 6 hr. Drugs were applied *i.p.* or orally (*p.o.*) just before the onset of the stress. The degree of erosions developed was evaluated as follows.

Erosion Index$=A+B$ (mm)

A: summation of the length of each erosion when it is 1 mm long or more.

B: product of 0.5 and number of each erosion when it is within 1 mm.

d) Effect on the Spontaneous Passage of Intestinal Content in Mice: Mice fasted overnight received drugs *i.p.* After 30 min of this application, each mouse was *p.o.* administered 0.5 ml of 40% $BaSO_4$ suspended in 2% CMC aqueous solution. Mice were killed by cervical dislocation 30 min after the test meal, followed by isolation of the intestine that was the portion from the duodenum to the appendix. The ratio of the leading edge of $BaSO_4$ to total length of the intestine was calculated.

e) Effect on the Rat Biliary Excretion: Rats were anesthetized as mentioned above and fixed on their back. The abdomen was opened and a thin polyethylene tube was proximally introduced into the bile duct. During 1.5 hr after the canulation the bile was collected, which served as control. Drugs were *p.o.* applied subsequently and the amounts of bile and its dried solid matter were measured hourly for succeeding 4 or 5 hr.

f) Effect on the Mouse and Guinea Pig Isolated Ileum: According to Magnus' method drugs were tested on the mouse ileum and the guinea pig ileum. The bath temperature was kept at 27°. Acetylcholine and histamine were used as contracting substances. Five to six trials were made in each dose of drugs.

Drug

Drugs used were as follows: Acetylcholine chloride, histamine dihydrochloride, atropine sulfate, diphenhydramine hydrochloride, propranolol hydrochloride, isoproterenol hydrochloride, glyceryl trinitrate, adrenaline hydrochloride and papaverine hydrochloride. Doses of drugs refer to the salt.

Result

1) Effects on the Cardiovascular System

a) Effects on Blood Pressure, Respiration, Peripheral Blood Flow and Heart Rate——The result in the dog is shown in Fig. 1 and Table I. CA scarcely affected them in a dose of

3) V.M. Rosenoer and H.O. Schild, *J. Physiol.* (London), **162**, 155 (1962).

4) S. Yano and M. Harada, *Japan. J. Pharmacol.*, **23**, 57 (1973).

1 mg/kg and exerted a fall in blood pressure and an increase of respiratory rate in doses of 5—10 mg/kg. Immediately after the administration of CA, a suppression of respiratory pressure occasionally took place for a short period prior to a respiratory stimulation. A fall in blood pressure was not affected with pretreatment of atropine, 10 μg/kg, diphenhydramine, 5 mg/kg, or propranolol, 1 mg/kg. These agents inhibited the hypotensive effect induced by acetylcholine, 2 μg/kg, histamine, 1 μg/kg, or isoproterenol, 1 μg/kg. A rise in blood pressure was occasionally observed after recovery of the hypotensive response as illustrated in Fig. 1 and Fig. 2 (CA 10 mg). Femoral blood flow increased in 5 out of 6 dogs. In general, the duration of this effect outlasted the recovery time of blood pressure lowering to the original level. Heart rate tended to increase simultaneously with a fall in blood pressure (about 2—8%), and thereafter it resumed the original rate or slightly decreased (within 5% in 10 min). In addition, a transient slight decrease in heart rate occasionally appeared immediately after the administration of CA. No change of electrocardiogram except a decrease in rate was recognized in a dose of 10 mg/kg. A fall in blood pressure was also observed in guinea pigs. The response was more sensitive than that of dogs, being positive in a dose of 1 mg/kg *i.v.* A fall in blood pressure by about 25% was obtained in 5 min in a dose of 5 mg/kg and recovered to the original level in 10 min. Heart rate was lowered by about 15% after 5 min of the application of 5 mg/kg. A transient rise in blood pressure was observed in some preparations.

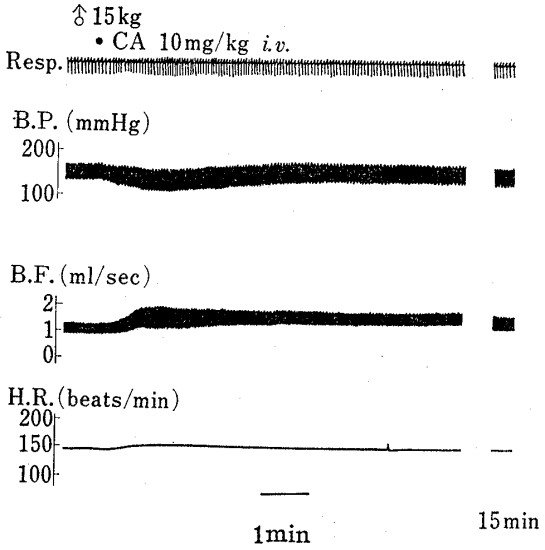

Fig. 1. Effect of Cinnamaldehyde (CA) on Blood Pressure(B.P.), Respiration(Resp.), Femoral Blood Flow (B.F.) and Heart Rate (H.R.) in an Anesthetized Dog

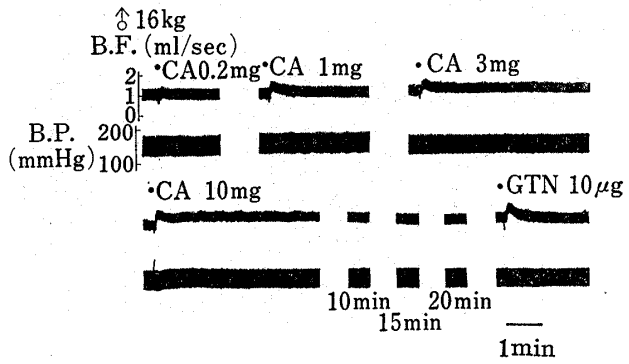

Fig. 2. Effect of Intraarterial Cinnamaldehyde (CA) on Femoral Blood Flow (B.F.) and Blood Pressure (B.P.) in an Anesthetized Dog

GTN: glyceryl trinitrate

TABLE I. Effect of Cinnamaldehyde on Blood Pressure and Femoral Blood Flow in Anesthetized Dogs

Dose (mg/kg, *i.v.*)	Blood pressure		Femoral blood flow[a)]	
	Decrease ratio (%)	Duration time (min)	Flow increase (ml/sec)	Duration time (min)
1	none	none	none	none
5	0—30	0—5	0—0.5	0—10
10	10—40	1—7	0—0.5	0—15

observation in 6 animals
a) basic flow: 1—2 ml/sec

CA increased femoral blood flow in an arterial administration as shown in Fig. 2. The effective doses of CA were 0.1—0.2 mg and more. The maximal vasodilatation induced by 10 mg of CA was approximately comparable with that of 10 μg of glyceryl trinitrate and lasted for about 15 min. No change in blood pressure was shown except a slight increase immediately after 10 mg of CA.

b) Effect on the Isolated Guinea Pig Hearts——i) Isolated Atria: Typical recordings are shown in Fig. 3. Generally the first application of CA caused an increase in amplitude, which lasted for several minutes in concentrations of 1×10^{-5}—1×10^{-4} g/ml. Repeated applications lessened an increase in amplitude, followed by an inhibition on the latter part of each trial in some preparations. There were some cases in which this inhibition occurred so rapidly that an increase in amplitude was obtained only in the first trial in the higher concentration of CA. About 1 min was needed for the development of such an increase, which was distinct from the immediate effect of adrenaline. Beating rate, on the whole, increased together with an increase in amplitude and decreased when the amplitude decreased. In order to know the specificity of the chemical structure with regard to the positive inotropic and chronotropic activities of CA, cinnamic alcohol and cinnamic acid (sodium salt) were tested on this preparation. Both substances caused no stimulating effect, which suggests the specificity of the aldehyde group in CA molecule.

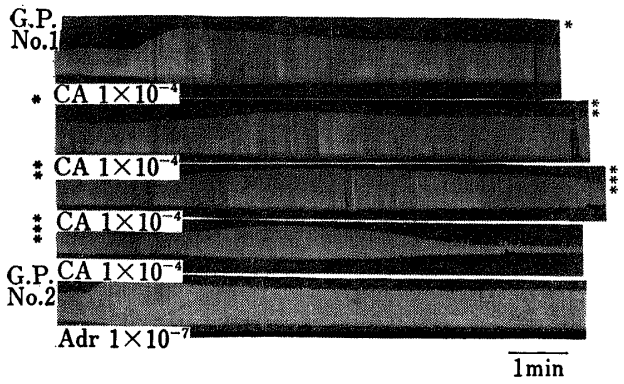

Fig. 3. Effect of Cinnamaldehyde on Isolated Atria from a Guinea Pig

CA: cinnamaldehyde, Adr: adrenaline
Numbers refer to the concentration (g/ml).
Asterisks indicate the order of the experimental trial.

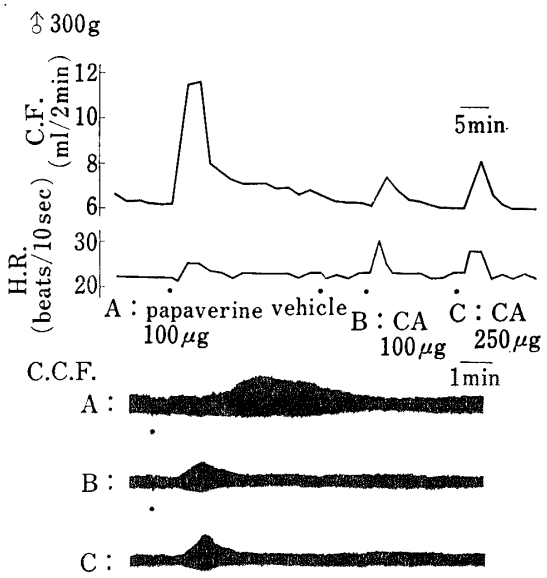

Fig. 4. Effects of Cinnamaldehyde (CA) on Coronary Flow (C.F.), Heart Rate (H.R.) and Cardiac Contractile Force (C.C.F.) in a Isolated Perfusing Heart from a Guinea Pig

ii) Isolated Perfusing Hearts: Typical recordings are presented in Fig. 4. CA in doses of 50—500 μg increased cardiac contractile force and heart rate. Such effects were generally lessened by repeated administrations. Arrhythmias were observed in such high doses as 250 μg and more. An increase in coronary flow was obtained although a quantitative evaluation of potency was difficult. Papaverine in doses of 100—200 μg also showed a remarkable increase in coronary flow either with positive inotropic and chronotropic effects or without them.

2) Effects on the Digestive System

a) Effect on the Rat Gastric Secretion——CA exerted no influence upon the pH value of the gastric perfusate in doses up to 10 mg/kg *i.v.*

b) Effect on the Rat Stomach Movement——Typical recordings are shown in Fig. 5. CA exerted inhibitory actions upon spontaneous gastric contraction in a dose of 5 mg/kg and upon gastric tone in a dose of 20 mg/kg *i.v.* The effects lasted for 5 min.

c) Effect on the Stress-induced Gastric Erosion in Mice——The result is shown in Table II. CA markedly protected against the generation of erosion in doses of 250 mg/kg *i.p.* and 500 mg/kg *p.o.*, respectively. This effect was dose-dependently observed.

d) Effect on the Spontaneous Passage of Intestinal Content in Mice——The result is given in Table III. CA, 250 mg/kg *i.p.*, significantly inhibited intestinal propulsion.

e) Effect on the Rat Biliary Excretion——The result is presented in Table IV. CA, 500 mg/kg *p.o.*, increased the excretion of total amounts of biliary solid matter as well as bile flow. This activity was displayed 1 hr after the administration of CA and lasted for 3—4 hr. The specific gravity of the biliary fluid after CA was not significantly different from that before CA.

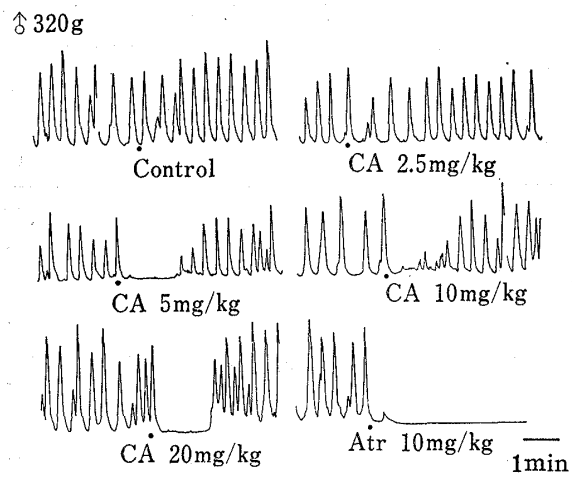

Fig. 5. Effect of Cinnamaldehyde on Movement of the Rat Stomach

CA: cinnamaldehyde, Atr: atropine
Drugs were administered *i.v.*

Table II. Effect of Cinnamaldehyde on Stress-induced Gastric Erosion in Mice

Treatment	Dose (mg/kg)	Route	No. of animals	Ulcer index
Control	—	*i.p.*	5	3.9±0.6[a]
Cinnamaldehyde	125	*i.p.*	4	3.5±0.8
Control	—	*i.p.*	5	6.6±1.3
Cinnamaldehyde	250	*i.p.*	5	0.5±0.5[b]
Control	—	*p.o.*	5	3.9±0.6
Cinnamaldehyde	250	*p.o.*	5	3.1±1.3
Control	—	*p.o.*	10	8.7±1.6
Cinnamaldehyde	500	*p.o.*	8	0.3±0.2[b]

stress: restraint and immersion (6 hr, 25°)
a) mean value ± standard error
b) significantly different from the control at $p<0.01$ (Fisher's method)

Table III. Effect of Cinnamaldehyde on Spontaneous Passage of $BaSO_4$ Meal in Small Intestine of Mice

Compound	Dose (*i.p.*) (mg/kg)	No. of animals	Passage rate (%)
Control	—	9	68.7±4.0
Cinnamaldehyde	62.5	4	70.4±5.4
Cinnamaldehyde	125	10	75.3±4.0
Cinnamaldehyde	250	7	38.1±7.1[a]
Neostigmine methyl sulfate	0.2	8	82.0±2.5[b]
Atropine sulfate	15	4	66.8±6.1
Atropine sulfate	30	5	57.9±5.0

a) significantly different from the control at $p<0.01$
b) significantly different from the control at $p<0.05$

Table IV. Effect of Cinnamaldehyde on Biliary Excretion in Rats

Treatment	Body weight (g)	No. of animals	Total amount of bile ± S.E. (ml)					
			−1.5—0[a] (hr)	0—1 (hr)	1—2 (hr)	2—3 (hr)	3—4 (hr)	4—5 (hr)
Control	381± 9	6	1.10 ± 0.10	0.49± 0.05	0.37± 0.05	0.34± 0.02	0.30± 0.03	
			1.037± 0.002[b]	1.040± 0.007		1.039± 0.003		
Cinnamaldehyde	400±18	6	1.08 ± 0.13	0.66± 0.05[c]	0.60± 0.07[c]	0.52± 0.05[c]	0.46± 0.05[c]	
			1.035± 0.002	1.036± 0.002		1.032± 0.002		
Control	261± 4	5	1.12 ± 0.07	0.59± 0.09	0.55± 0.09	0.46± 0.05	0.42± 0.05	0.39± 0.04
			1.038± 0.006	1.033± 0.004			1.033± 0.003	
Cinnamaldehyde	260± 6	5	1.10 ± 0.06	0.90± 0.09[c]	0.72± 0.07	0.60± 0.05	0.50± 0.05	0.40± 0.02
			1.035± 0.003	1.032± 0.003			1.025± 0.003	

a) Period of collection, Drugs were administered at 0 hr.
b) specific gravity ±S.E.
c) significantly different from the control at $p < 0.05$

f) **Effect on the Mouse and Guinea Pig Isolated Ileum**——CA slightly decreased the basal tone of the mouse and guinea pig ileum in a concentration of 1×10^{-4} g/ml. Both acetyl choline- and histamine-induced contractions were inhibited by CA in the similar manner to the case with papaverine. In three kinds of the experimental preparations, namely, the mouse ileum treated with acetylcholine, the guinea pig ileum treated with acetylcholine and the guinea pig ileum treated with histamine, the potency of CA was about 7—10% of that of papaverine to produce 50% inhibition of the maximal contraction induced by the agonists.

Discussion

A fall in blood pressure was accompanied by a respiratory stimulation and an increase in heart rate, which suggests that a reflex effect operated for the latter two physiological changes. A mild vasodilating activity was obtained in the dog hind limb. This vasodilatation had the following characteristics: it was not so transient as glyceryl trinitrate or papaverine and the effect persisted beyond the period of a fall in blood pressure by *i.v.* administration of CA. A papaverine-like musculotropic activity of CA which is to be mentioned below seems to participate in its vasodilating action. CA exerted an inhibitory action on heart rate in the *in vivo* preparation except a possible stimulation through the reflex. Since atropine, diphenhydramine and propranolol failed to antagonize the fall in blood pressure induced by CA, the mild vasodilating action is inferred to contribute to the fall in blood pressure. Rise in blood pressure induced by CA, which was occasionally observed in the present study and was sometimes displayed in curarized rabbit (unpublished data), remains to be investigated.

The cardiac effect of CA on two kinds of preparation of the isolated guinea pig heart was either stimulative or inhibitory according to the number of the drug application, isolated atria being more sensitive for the inhibition. The repeated applications of CA led to disappearance of the stimulative activity and the predominance of the inhibitory activity. The presence of a lag time for the cardiac activation suggests an indirect action of CA on the

preparation. The direct vasodilating effect of CA may participate in the increase in coronary flow. A structural specificity of the functional group in CA molecule was recognized for the cardiac stimulation.

CA inhibited both the rat stomach movement and the mouse intestinal propulsion. The former inhibition, however, was transient and the latter one was displayed in a relatively high dose, which suggests that the effects of CA on gastrointestinal movement are relatively weak. In the experiments on the isolated mouse and guinea pig ileum CA showed a papaverine-like musculotropic action. A remarkable protective effect of CA against stress-induced erosion in the mouse stomach was observed especially after 500 mg/kg *p.o.* of CA. The stomach remained in a relaxed state to some extent. We have obtained a suggestion that inhibition of stomach movement may induce a protection against stress-induced erosion.[5] It is inferred that mild suppression of the stomach movement may play a part in the protective action of CA. Further study remains to be carried out on this problem. CA increased biliary excretion with an effective period of 3—4 hr.

The opinion that essential oils contained in chinese cinnamon, of which CA is a main component, are intimately related to pharmacological or therapeutic effects of this crude drug was discussed in the previous paper. Although the effects of CA on the digestive systems through the gustatory and olfactory organs were not examined, it is suggested that pharmacological gastrointestinal effects of CA observed in the present study may contribute to therapeutic actions of chinese cinnamon on the digestive system.

In chinese medicine, chinese cinnamon is used for palpitation, headache, feeling of rush of blood to the head, fever, pain of extremities and so on. The peripheral vasodilating action of CA is supposed to participate in antipyretic and hypothermic effects, as is shown in the previous paper. This finding seems to be coincided with the fact that chinese cinnamon is used for febrile symptoms. Moreover, this action may be favorable to relieve pains of human extremities which chinese cinnamon is often prescribed for.

Acknowledgement We are grateful to Messrs. Y. Fujii, J. Kamiya, S. Maeda, and M. Akahane for their technical assistance.

5) M. Harada and S. Yano, *Oyo Yakuri*, **8**, 1 (1974).