Effects of steamed ginseng radix on blood pressure in hypertensive rats

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Abstract

The effects of steamed ginseng radix (Korean red ginseng powder, GP) on blood pressure (BP) were determined acutely and chronically in normotensive and hypertensive rats. In the acute experiment, GP (350mg/kg, *p.o.*) was given to stroke-prone spontaneously hypertensive (SHRSP) rats and deoxycorticosterone-salt hypertensive (DOC) rats. Mean BP was determined continuously for 5h and after 24h in unanesthetized condition. GP showed no significant acute effects on BP in these hypertensive rats. In the chronic experiment, GP mixed into chow was given for 11 weeks to normotensive Donryu strain, spontaneously hypertensive, two kidney, one clip hypertensive, severely or mildly hypertensive DOC and SHRSP rats. Doses ranged from 250 to 700mg/kg per day. GP slightly decreased tail BP determined indirectly in mildly hypertensive DOC and SHRSP rats within 10 weeks. However, there were no statistically significant differences in mean BP, determined directly without anesthesia or restraint at the 11th week, between the GP treated and control groups of all types of rats. Prewarming and restraining are necessary for the indirect BP determination at the tail, and affects BP of the rat in some way. Therefore, it is suggested that GP has no appreciable effects on BP in normotensive and hypertensive rats in the chronic experiment. This is also supported by the fact that GP showed no significant preventive effects on the development of vascular lesions and nephrosclerosis, and did not significantly affect plasma renin concentration (PRC) in hypertensive rats in the chronic experiment.

Keywords blood pressure, steamed ginseng radix, heart rate, hypertensive rats, plasma renin concentration, vascular disease, *Panax ginseng* C.A.Meyer

Abbreviations BP ; blood pressure, BW ; body weight, CLIP ; two kidney, one clip hypertensive rats, DOC ; deoxycorticosterone-salt hypertensive rats, DOC(m) ; mildly hypertensive DOC rats, DOC(s) ; severely hypertensive DOC rats, DON ; HOS® ; Donryu strain rats, GP ; steamed ginseng radix (Korean red ginseng powder, Korai Kosanfun®, Japan Korea Red Ginseng Co.), HR ; heart rate, PRC ; plasma renin concentration, SHR ; spontaneously hypertensive rats, SHRSP ; stroke-prone SHR rats

Introduction

In regards to the effects of ginseng radix (roots of *Panax ginseng* C.A.Meyer) on blood pressure (BP), there were twocontroversial opinions.[1] Many people considered ginseng unfavorable for hypertensive patients.[1] Some other people considered that ginseng has antihypertensive activity.[1]

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Sohn et al. reported that, in essential hypertension, ginseng extract (1g per day, *p.o.*) shows antihypertensive effects within a week after the administration had started and for 12 weeks thereafter.[1] Kaneko et al. reported acute hypotensive effects of steamed ginseng radix (Korean red ginseng powder, GP) (4.5g, *p.o.*) in healthy adults.[2]

Siegel reported that several ginsengs, including *Panax ginseng*, shows hypertensive effects in ginseng users.[3] However, these clinical studies were not carried out with fully rational experimental designs.

In anesthetized dogs, cats, rats or rabbits, the primary effect of ginseng extracts is depressor.[4,5] Wood et al. reported that, in anesthetized dogs, the effect of *Panax ginseng* extract (10 ~20mg/kg, *i.v.*) shows depressor followed by pressor action.[5]

Panax ginseng was shown to contain several saponin fractions which produce depressor or pressor effects in anesthetized rats.[6-8] Furthermore, sustained depressor effect is produced by steamed ginseng extract but not by dried ginseng extract, in cats and rabbits.[9]

Sohn et al. indicated that, in chronic studies for 6 weeks with spontaneously hypertensive (SHR) rats, ginseng extract has hypertensive effects when it is given in small amounts (5 mg/kg per day, *i.p.*).[1,10] To obtain antihypertensive effects, a relatively large amount of ginseng extract (more than 10 mg/kg per day, *i.p.*) was required.[1,10] They also indicated that plasma renin activity is decreased after ginseng treatment in parallel with BP decrease.[10] The mode of action of ginseng to BP by oral administration was almost the same as seen by intraperitoneal injection.[1] However, the antihypertensive effect by oral administration lasted during the total period of observation, whereas it lasted only temporalily by intraperitoneal injection.[1] Minami et al. reported that San-chi ginseng (roots of *Panax pseudo-ginseng* Wall) in chow (500mg/kg per day, *p.o.*) suppresses the development of hypertension in stroke-prone SHR (SHRSP) rats within a week.[11] Kuwaki reported that *Panax ginseng* extract in drinking water shows a tendency to accelerate the development of hypertension in SHRSP rats within 16 weeks.[12]

As shown above, the effects of ginseng on BP in man and animal has not been fully clarified. Further systematic studies are required to establish if ginseng has antihypertensive action. In this study, we have investigated acute and chronic effects of steamed ginseng radix (Korean red ginseng powder, GP) in four different types of hypertensive rats : SHR,[13] SHRSP,[14] deoxycorticosterone-salt (DOC), and two kidney, one clip (CLIP) hypertensive rats with normotensive Donryu strain (DON).

Materials and Methods

Experimental Design——Present study consists of two major parts, acute and chronic experiments. In the acute study, a total of 4 experimental groups, with 5 rats in each, were made with combinations of SHRSP and DOC rats and GP. Crossover experiments were carried out one week after the first experiments. Twelve groups, with 7-11 rats in each, were made with combinations of normotensive Donryu strain (DON), SHR, CLIP, severely (DOC(s)) in the first series, and mildly (DOC(m)) hypertensive DOC, and SHRSP rats in the second series with or without GP treatment in the chronic experiments. Student's t-and χ^2-tests were used for statistical analyses.

Rats——HOS® : Donryu strain (DON) rats were female and 7-9 weeks of age, weighing 110-200g. SHR rats were female and 7-8 weeks of age, F39 from the colony of the Department of Pharmacology, Jichi Medical School, weighing 100-130g. SHRSP rats were male and 10-12 weeks of age, F60 from the colony of the same institute, weighing 180-220g. CLIP rats were made by constriction of the left renal artery with a silver ribbon (slit width 0.2mm) and leaving the contralateral kidney intact in DON rats. GP treatments were started 7 weeks after the surgery. DOC(s) and DOC(m) rats were made by left nephrectomy, giving 1% NaCl solution as drinking fluid, and treating with deoxycorticosterone acetate (8mg/kg per week, *s.c.*) for 6 and 5 weeks, respectively, in DON rats. GP treatments were started 7 and

6 weeks after the surgery in DOC(s) and DOC(m) rats, respectively. Doses of deoxycorticosterone were reduced to 5-7 mg/kg per week for the first 5-6 weeks and none thereafter in DOC(s) rats after GP treatments had started. They were reduced to 3 mg/kg per week for 11 weeks in DOC (m) rats.

Determination of Blood Pressure and Heart Rate——In the acute experiment, the mean blood pressure (BP) was determined directly without anesthesia or restraint through a cannula inserted into the abdominal aorta.[15] After the control determination of BP for 15min before GP administration, BP was recorded continuously for 5h and the value at 24h was taken separately. BP values were read every 0.5h for 4-5h after the treatment. In the chronic experiments, tail BP and heart rate (HR) were determined by rat tail manometer-tachometer systems (Natsume KN-209 in the first series or KN-210 in the second). Tail BP and HR were determined without anesthesia after prewarming the rats at 50℃ for 3min. Tail BP obtained by KN-209 and KN-210 have been shown to be identical with mean and maximum BP, respectively (unpublished data). Tail BP and HR were determined once a week during the week before and for 10 weeks after the GP treatments had started. At the end of the experiments, during the 11th week, mean BP was determined directly as described above.

GP Treatments——Steamed ginseng radix (Korean red ginseng powder, GP) (Korai Kosanfun®, Japan Korea Red Ginseng Co.) was suspended in 1% NaCl solution containing 0.5% carboxymethyl cellulose (Wako Pure Chemical) at a volume of 5 ml/kg body weight, and was administered orally by a gastric tube at a dose of 350mg/kg in the acute studies. Carboxymethyl cellulose-saline solution was given to the control group. In the chronic studies, GP was mixed into chow (Nihon Nosan MR-3-A) at an amount of 5.0 g/kg, and was given *ad libitum* for 11 weeks. Doses were calculated from food intake, and were 250-700 mg/kg per day. Regular chow was given to the control group.

Determination of Plasma Renin Concentration and Postmortem Examination——In the chronic studies, a blood sample of 0.5ml was obtained following BP determination through the aortic cannula, and used for determination of PRC. PRC was determined by the modified method of Carvalho et al.[15] The rat was then sacrificed with ether, and inspected macroscopically. The heart and kidney were weighed.

Results

A. Acute Effects of GP in Hypertensive Rats (Fig. 1, 2)

In SHRSP and DOC rats, mean BP of the control group decreased gradually for the first 4-5h and recovered after 24h. GP treatments (350mg/kg, *p.o.*) showed no significant effects on BP in

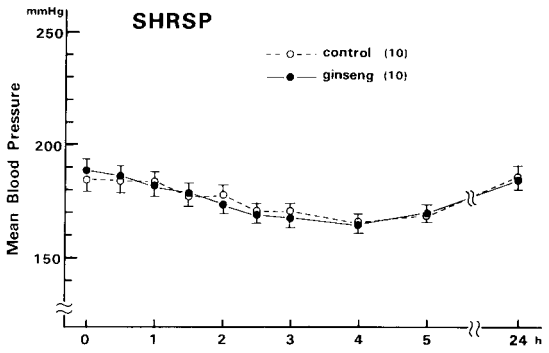

Fig. 1 Acute effects of GP on mean BP in SHRSP rats. Vertical bars are S.E. of the mean. No. of rats in each group is shown in parentheses following explanatory symbols. GP (350mg/kg, *p.o.*) was administered at 0 h.

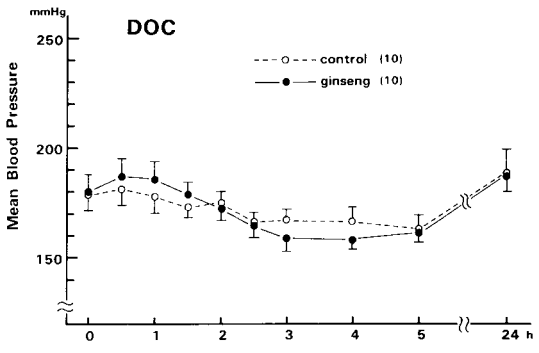

Fig. 2 Acute effects of GP on mean BP in DOC rats. Details are the same as in Fig. 1.

SHRSP rats. In DOC rats, GP treatments showed a tendency to increase mean BP for the first 1.5 h and decrease it at 3-4 h after administration, compared to the control. However, there were no statistically significant differences between the GP treated and control groups.

B. Chronic Effects of GP in Hypertensive Rats

Body Weight, Food and Fluid Intakes——The body weight (BW) of the control and GP groups increased at approximately an equal rate in DON, SHR, CLIP and DOC(m) rats for 11 weeks. In DOC(s) and SHRSP rats, GP treatments significantly decreased BW, compared to the control, at the 9th and 1st-2nd week, respectively.

The food intake of the control groups decreased gradually in DON and SHR rats, and was fairly constant in CLIP, DOC(s), DOC(m) and SHRSP rats for 11 weeks (Fig. 3). GP treatments significantly decreased food intake, compared to the control, at the 7th-10th, 7th-8th or 10th, 5th-6th or 9th, 2nd-5th or 8th-10th, and 1st week in DON, SHR, DOC(s), DOC(m) and SHRSP rats, respectively. GP treatments significantly increased it, compared to the control, at the 7th-8th or 10th week in CLIP rats.

The fluid intake of the control groups decreased gradually in DON and DOC(m) rats, and was fairly constant in SHR and CLIP rats for 11 weeks. In DOC(s) and SHRSP rats, it decreased for the first 4 and 2 weeks, respectively, and increased thereafter. GP treaments significantly increased the fluid intake, compared to the control, at the 3rd-4th, 1st-8th, 2nd-10th, 8nd-10th and 1st-8th week in DON, CLIP, DOC(s), DOC(m) and SHRSP rats, respectively. GP treatments significantly decreased it, compared to the control, at the 7th and 1st-4th week in DON and DOC (m) rats, respectively.

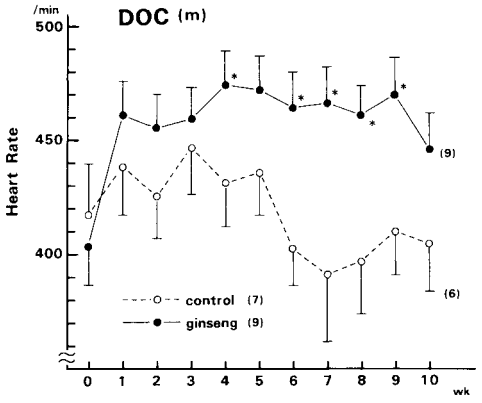

Fig. 4 Chronic effects of GP on HR in DOC(m) rats. Details are the same as in Fig. 3.

Heart Rate (Fig. 4)——The control groups given the normal chow showed fairly constant HR values during the experiments in DON, SHR, CLIP, DOC(s) and SHRSP rats. GP treatments

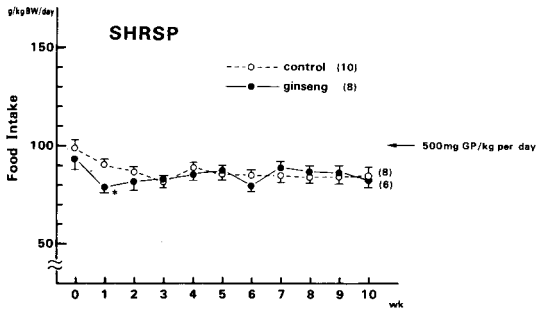

Fig. 3 Chronic effects of GP on food intake in SHRSP rats.

Vertical bars are S.E. of the mean. Initial and final No. of rats in each group are shown in parentheses following explanatory symbols and at the last week of the observation, respectively. *Indicates statistically significant difference ($P<0.05$), compared to control.

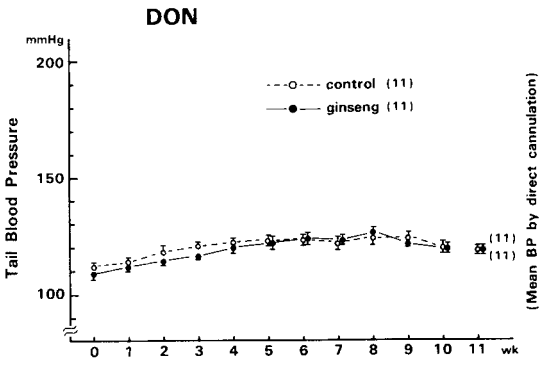

Fig. 5 Chronic effects of GP on BP in normotensive DON rats.

Tail BP was determined by a rat tail manometer-tachometer system (Natsume KN-209). Other details are the same as in Fig. 3.

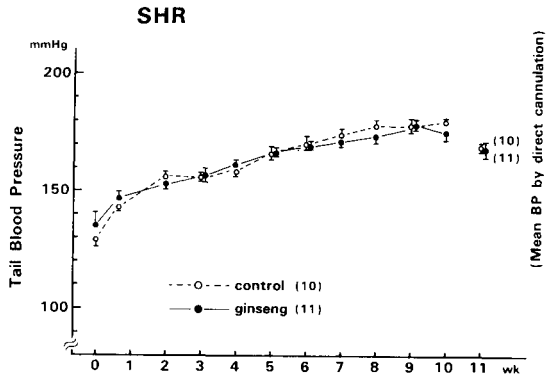

Fig. 6 Chronic effects of GP on BP in SHR rats. Details are the same as in Fig. 5.

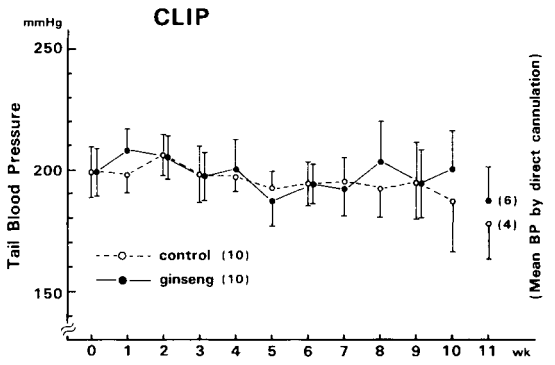

Fig. 7 Chronic effects of GP on BP in CLIP rats. Details are the same as in Fig. 5.

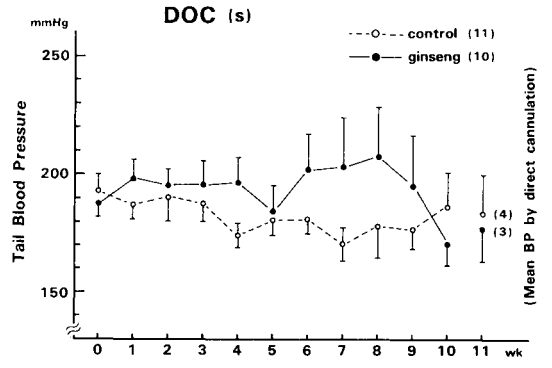

Fig. 8 Chronic effects of GP on BP in DOC (s) rats. Details are the same as in Fig. 5.

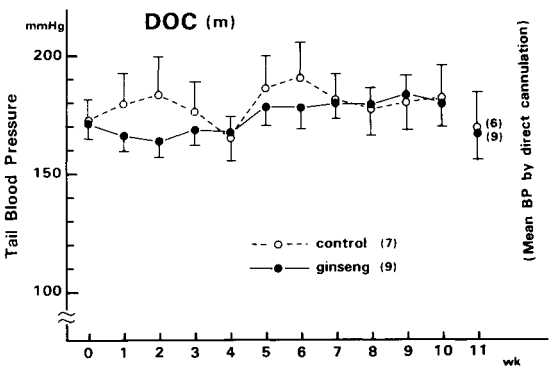

Fig. 9 Chronic effects of GP on BP in DOC(m) rats. Tail BP was determined by a rat tail manometer-tachometer system (Natsume KN-210). Other details are the same as in Fig. 3.

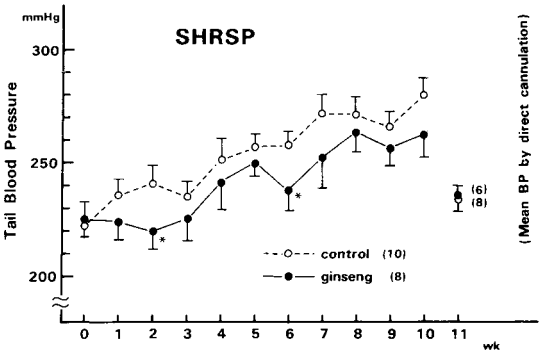

Fig.10 Chronic effects of GP on BP in SHRSP rats. Details are the same as in Fig. 9.

significantly increased HR, compared to the control, at the 3rd or 6th and 4th-9th week in DOC(s) and DOC(m) rats, respectively. GP treatments showed no significant effect on HR in other groups.

Blood Pressure (Fig. 5-10)——Tail BP of the control groups increased gradually in SHR and SHRSP rats, was fairly constant in DON, CLIP and DOC(m) rats, and decreased in DOC(s) rats due to the early death of rats with very high BP during 10 weeks. Therefore, the GP treated group of DOC(s) rats showed slightly higher BP than the control, except at the 10th week, before which rats with relatively higher BP died. GP treatments showed a tendency to decrease tail BP in DOC(m) and SHRSP rats, compared to the

control. GP significantly decreased tail BP, compared to the control, at the 2nd and 6th week in SHRSP rats. In other groups of rats, GP showed no significant effect on tail BP for 10 weeks. However, mean BP of the GP group, determined directly at the 11th week, was almost identical with that of the control in all six types of rats investigated in the chronic study.

Plasma Renin Concentration and Findings at Postmortem Examination——GP treatments increased PRC in CLIP rats, and decreased it in SHRSP rats, although the differences were not statistically significant, compared to the control (Table I). There was a significant correlation between PRC and mean BP in DOC(m) rats ($r^2 = 0.804$). GP showed no significant effects on PRC in other types of rats. Vascular lesions like polyarteritis nodosa and nephrosclerosis, which are usually observed in hypertensive rats, were not seen macroscopically in DON and SHR rats. GP treatments did not significantly decrease incidences of vascular lesions in the mesenteric area or brain and nephrosclerosis in CLIP, DOC(s), DOC(m) and SHRSP rats. The kidney and heart weights were not significantly affected by GP treatments in all six types of rats.

Table I Effects of ginseng on plasma renin concentration

Rat	Treatment	No. of Rats	PRC angiotensin I formation ng/ml per h	P
DON	control	11	17.7± 2.8[a]	
	ginseng	11	19.0± 1.7	NS[b]
SHR	control	10	11.6± 0.7	
	ginseng	11	14.9± 1.9	NS
CLIP	control	4	89.6± 42.3	
	ginseng	6	291.3± 157.1	NS
DOC(s)	control	4	8.2± 0.9	
	ginseng	3	7.9± 1.2	NS
DOC(m)	control	6	3.2± 1.5	
	ginseng	9	2.9± 1.1	NS
SHRSP	control	8	50.1± 3.0	
	ginseng	6	35.6± 9.3	NS

a: Mean ± SE. b: Statistically not significant compared to control.

Discussion

In our second series of experiments, the acute effects of GP on BP were examined in SHRSP and DOC rats. GP showed no significant effects on BP for 24h in these hypertensive rats. Kaneko et al. reported acute hypotensive effects of GP in healthy adults.[2] However, their experimental design did not include any control group. In anesthetized animals, the primary effect of ginseng extracts given intravenously is depressor.[4,5] However, the experimental conditions, such as the route of administration and time of observation, are very different from ours.

In our first series of chronic studies, the GP treated group of DOC(s) rats showed slightly higher tail BP than the control due to the early death of rats with very high BP in the control group during 10 weeks. Therefore, in the second series, the chronic effects of GP on BP were re-examined in DOC(m) rats. SHRSP rats were also used to investigate the effects of GP in malignant hypertension. GP treated groups in DOC(m) and SHRSP rats showed lower tail BP than the control within 10 weeks. It may be possible that GP prevented the increase of tail BP induced by prewarming and restraining stresses in DOC(m) and SHRSP rats. GP treatments increased HR and fluid intake in DOC (s) and DOC (m) rats, which seemed not to affect BP largely.

In the chronic studies, there were no statistically significant differences in mean BP, determined directly without anesthesia or restraint at the 11th week, between the GP treated and control groups of all six types of rats. Mean BP must be more reliable than tail BP, because prewarming and restraining are necessary for the indirect BP determination at the tail, and affects BP of the rat in some way. Therefore, it was suggested that GP showed no appreciable effects on BP in normotensive and hypertensive rats in chronic experiments. This is also supported by the fact that GP showed no significant preventive effects on the development of vascular lesions and nephorsclerosis, and did not significantly affect PRC in hypertensive rats in chronic experiments.

Discrepancy between the results of this and previous studies by Sohn et al.[1,10] and Kuwaki[12] may be caused by the differences in ginseng materials or the method of BP determination.

They had used ginseng extracts and determined BP only by indirect methods. We have used steamed ginseng in powder, because it is easy to obtain and clinical studies have been reported on it.[2] Components of steamed ginseng in powder must be different from those of ginseng extracts. Therefore, it remains possible that some ginseng extracts have significant effects on BP in hypertensive rats. In conclusion, however, steamed ginseng in powder (GP) has no appreciable acute or chronic effects on BP in hypertensive rats studied.

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