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Effect of Ginseng Components on the Potassium Depleted Cardiomyopathic Rats and it's Mechanism of Action

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Abstract □ The effect of ginseng components on the potassium depleted cardiomyopathic rat heart was investigated. In the perfused heart experiment using Langendorff apparatus, the deterioration rate of contractile force of potassium depleted rat heart (low potassium diet group) was faster than that of normal rat heart and ginseng components showed the ability to slow the deterioration rate of potassium depleted hearts. Both sialic acid contents in sarcolemmal ghost and sialyltransferase activity of 40,000×g subcellular fraction prepared from cardiac ventricular tissue of low potassium diet group were significantly decreased compared to those of normal group. The decrease of the sialic acid content and sialyltransferase activity in sarcolemma of low potassium diet group was inhibited when ginseng was concomitantly administered. Calcium uptake of sarcoplasmic reticulum prepared from low potassium diet group was significantly greaterthan that of normal group. Ginseng extract or total saponin showed the tendency to inhibit the increase of calcium uptake.

Keywords □ Ginseng, Cardiomyopathy, Potassium depletion, Rat.

Panax ginseng has been known as a tonic agent in traditional oriental medicine and believed to play an important role in maintaining the homeostatic mechanism under the stressful conditions.[1] It is stated in "Chinese Medicinal Herbs" that ginseng strengthens the function of the heart.[2] It was demonstrated that the deterioration of the contractile force was slower in hearts from ginseng extract treated rats than in untreated rats.[3] A similar phenomenon was exhibited in the hearts of rats treated with total saponin of ginseng and ginsenoside Rbl, but ginsenoside Re was found not to show any significant effect.[4] Ginseng also increased both the maximum velocity (V_{max}) of isotonic shortening and isometric force (Po) of cardiac muscle significantly at all afterload.[4] Considering the afore-mentioned results, it is expected that cardio-effect of ginseng might be more obvious in pathological states than in normal state. Therefore, it was attempted to investigate the effect of ginseng ethanol extract or ginseng total saponin on potassium depleted cardiomyopathic rat hearts.

EXPERIMENTAL METHODS

The Diets

The normal diet was prepared according to the formula[5] of AIN-76 TM purified diet recommended by Ad Hoc Committee of the Council of the American Institute of Nutrition (AIN). Potassium deficient diet had the same composition as the normal diet, except for potassium sources which were replaced by corn starch or other metal ion such as sodium. Potassium content of the normal diet was found to be 0.5% which is sufficient for potassium source and potassium content of the potassium deficient diet was found to be no more than 0.05%.

Ginseng Ethanol Extract and Ginseng Total Saponin

Ginseng ethanol extract was prepared by ext-

racting the crushed red ginseng root with 70% ethanol at 70°C. Ginseng total saponin was made by the method of Shibata[6] and Namba [7,8].

Experimental Animals

Three-week old Sprague-Dawley male rats were selected at the start of the experiment. They received normal diet until their body weights were reached upto about 150 g, then were divided into the following groups, each consisting of 10 to 25 rats: A. received normal diet; B. received potassium deficient diet; C. received the potassium deficient diet and daily 100 mg/kg of ginseng ethanol extract p.o. for one or two weeks; D. received the potassium deficient diet and daily 50mg/kg of ginseng total saponin p.o. for 2 weeks. Distilled water was provided *ad libitum* as drinking water for all groups.

The Body Weight and Heart Weight

The body weight of rats in each group were weighed at every week through whole experimental period. Hearts were removed at the end of the experiment and weighed. Heart weight ratio to body weight is calculated for each rat.

Determination of Blood Pressure

Systolic blood pressure of each rat was measured by indirect method at tail artery with physiograph (Narcotrace 80).

Potassium Concentration in Heart Ventricular Tissue and Serum

Deproteinized serum was diluted with distilled water and potassium concentration was determined by ICP-emmission Spectrophotometry (Plasmascan model 710). Immediately after the blood collection, heart was removed and perfused with ice-cold saline solution through aorta to wash out the remaining blood in ventricle and coronary blood vessels. After ventricular portion was cut out, it was blotted with filter paper and weighed, each ventricular tissue was transferred into a crucible with a few drop of sulfuric acid and ashed at 400°C. for 5 hours in a furnace. The sulfated ash thus obtained was dissolved in distilled water and the potassium content was measured by the same method as for serum.

Contractile Force of Perfused Heart in Langendorff Apparatus

Rats were killed by a blow on the head and their hearts were rapidly removed. Immediately after extraneous tissues were removed, the hearts were perfused with modified Krebs-Henseleit buffer in Langendorff apparatus and contractile force was recorded on physiograph according to the method of Kim *et al.*[3] with following electrical stimulating conditions; frequency, 330 beats per minute, duration, 10 msec., voltage, square wave with 2 times of minimum threshold.

Sarcolemmal Sialic Acid Content

The fragments of sarcolemmal ghosts were prepared from rat heart ventricle by the method described by Katz,[9] and were hydrolyzed with 1 N-H_2SO_4 for 60 minutes at 80°C. Sialic acid content in the hydrolysate was determined by thiobarbituric acid assay method of Warren[10] and protein concentration in the sarcolemmal preparation was measured by Lowry method.[11]

Preparation of Subcellular Fractions

Approximately 2 grams of minced ventricular tissue were suspended in 5 volumes of an ice-cold imidazole-EDTA buffer (imidazole, 2.5 mM, EDTA, 0.1 mM, pH 7.4) and homogenized in a universal homogenizer (Nihon Seiki) with full speed for 30 sec 3 times with a rest interval of about 60 sec. The homogenate was centrifuged at 100×g for 2 minutes and the supernatant was recentrifuged at 7,000×g for 10 min. The 7,000×g supernatant was centrifuged at 40,000 ×g for 60 min. Thus the 100×g pellet, 7,000 ×g pellet, 40,000×g pellet and 40,000×g supernatant were obtained.

Sialyltransferase Activity

Sialyltransferase activities in sarcolemma and the subcellular fractions were measured as described by Bernacki[12] in a total volume of 200 μl containing 100 ul of tissue protein suspension (2-5 mg as protein), 25 μl of 80 mM $MgCl_2$ solution, 50 μl of 1% asialofetuin in 20 mM Tris buffer (pH 7.4) as exogenous acceptor[13,14] and 25 μl of 1.2×10 M CMP-(14C) N-acetyl neuraminic acid (Sialic acid, 166 mCi/mol, New England Nuclear). Reactions were carried out for 1 hr. at 37°C and were terminated by the addition of 2ml of 1% phosphotungstic acid in 0.5 N HCl. Acid precipitation obtained by centrifugation were washed twice with 2 ml of 10% trichloroacetic acid and once with 2 ml of ethanol-ether (2:1 v/v) mixture.

The resultant precipitate was dissolved in 0.5 ml of Protosol (tissue solubilizer, NEN) and added into 10 ml of toluene based cocktail containing 0.55% PPO, 0.0001% POPOP and 33.3 % Triton X-100. Samples were counted in a liquid scintillation counter (Beckman LS 7500) with counting efficiencies for 14c of above 80%. Enzyme activity was calculated and represented as n moles of sialic acid incorporated/mg tissue protein/hr.

Calcium Uptake by Sarcoplasmic Reticulum from Ventricular Tissue.

Sarcoplasmic reticulum (SR) fractions were prepared from heart ventricular tissue as the method described by Schwartz[15] and Sulakhe.[16] SR calcium uptake was measured in the presence of 5 mM KCl, 10mM $MgCl_2$, 4 mM tris-ATP, 20 mM tris-maleate buffer (pH 6.8), 100 μM $CaCl_2$, containing ^{45}Ca (0.03 μCi/ml) and 20-60μg/ml of SR protein in a total volume of 6 ml.

The reaction was started by the addition of ATP after one minute preincubation period. After incubation at 37°C and at selected times, an aliquot (1ml) was treated by millipore membrane filter (HA type, pore size 0.45 μm) technique.

Calcium uptake was estimated from the radioactivity of the filtrate and represented as μmoles calcium/mg protein. Bray's solution (100 mg methanol, 20 ml ethylene glycol, 60g naphthalene, 4g PPO, 0.02g POPOP and p-dioxane added to make 1,000 ml) was used as scintillation cocktail.

RESULTS

Effect of Ginseng Components on Body Weight and Heart Weight

Figure 1. shows the growth curve of rats fed normal diet from 3 week-old to 6 week-old and thereafter normal diet and potassium deficient diet or ginseng components. The weight gain of rats fed potassium deficient diet was much less than that of normal diet group. Concurrent administration of ginseng ethanol extract or ginseng total saponin with potassium deficient diet did not influence the growth rate. The body weight of the potassium-deficient rats and potassium-deficient diet plus ginseng declined significantly. The heart weight was also less in the potassium deficient animals. As a result, the heart weight/body weight ratio in these animals

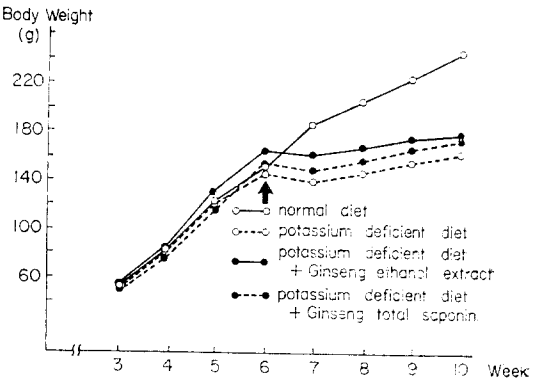

Fig. 1. Growth curves of control and variously treated rats.

Table I. Body weights and heart weights and ratios of heart weight to body weight of control and treated rats.

Rats	No. of animals	Body weight(g)	Heart weight(mg)	Ratio(%)
Normal diet	8	230.0±19.0	794.5±54.1	0.35
K-deficient diet	11	182.6± 5.2*	609.7±11.7*	0.34
K-deficient diet+Ginseng ethanol extract	11	187.9± 9.8*	633.5±25.4	0.34
K-deficient diet+Ginseng total saponin	11	192.3± 8.5	647.6±27.6*	0.34

Data are given as Means±S.E. Significantly different from control; *$p<0.05$

Table II. Systolic blood pressure of control and treated rats.

Rats	No. of animals	Blood pressure(mmHg)
Normal diet	5	126.0±5.6
K-deficient diet	4	121.3±6.4
K-deficient diet+Ginseng ethanol extract (2 weeks)	5	120.4±3.9
K-deficient diet+Ginseng ethanol extract (1 week)	5	128.9±7.8

Data are given as Means±S.E.

Table III. Potassium concentration of serum and heart ventricular tissue from control and treated rats.

Rats	No. of animals	Potassium concentration	
		Ventricular tissue (μEq/g. Ventricle)	Serum(μEq/ml)
Normal diet	11	66.9±2.2	5.24±0.15
K-deficient diet	11	61.2±2.1	3.77±0.11***
K-deficient diet+Ginseng ethanol ext.	11	61.1±2.4	4.59±0.23*
K-deficient diet+Ginseng ethanol ext. (1 week)	10	62.7±2.3	4.22±0.21

Data are given as Means±S.E. Significantly different from control; *$p<0.05$, ***$p<0.001$

did not change significantly (Table I).

Effect on Systolic Blood Pressure

As can be seen from Table II, the systolic blood pressures of rats in each experimental group showed no signficant differences.

Effect on Potassium Concentration in Serum and Ventricular Tissus

Potassium concentrations in serum and heart ventricular tissue are summarized in Table III. The rats on the potassium deficient diet for 2 weeks exhibited significantly ($p<0.001$) lower potassium content than the normal diet group. When the ginseng ethanol extract (100mg/Kg) was administered orally for 2 weeks concomitantly with potassium deficient diet, potassium concentration in serum was significantly ($p<0.05$) increased compared to the potassium deficient diet group, while in one week-administration group showed the similar tendency without statistical significance. On the other hand, there was no significant difference among the potassium contents in heart ventricular tissue of all the experimental groups.

Effect on the Contractile Force of Perfused Heart in Langendorff Apparatus

Deterioration rates of the contractile force of perfused rat hearts in Langendorff apparatus are shown at Figure 2. Contractile force of isolated

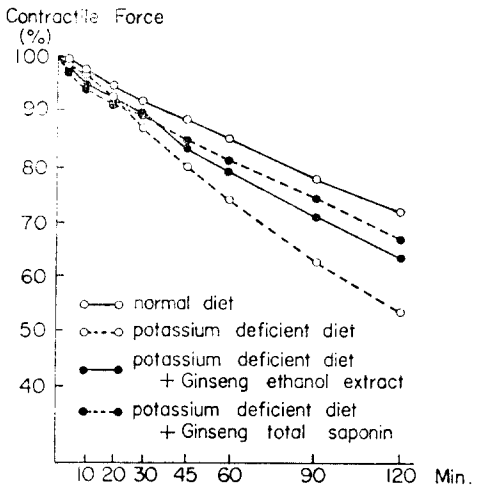

Fig. 2. Deterioration rate of the contactile force in excised heart from control and treated rats.

hearts from the potassium deficient diet treated rats was decreased to the level of 53.6% of their initial force after 120 minutes of perfusion, whereas the contractile force of normal diet group was maintained at 71.7% of their initial strength after the same period. When ginseng ethanol extract was concurrently administered for 1 week or 2 weeks with potassium deficient diet, the contractile force of the isolated hearts deteriorated slower compared to that of potassium deficient diet treated group.

Sialic acid Content in Sarcolemmal Fragments

The sialic acid content in the sarcolemmal ghost prepared from heart ventricular tissue of the rats fed potassium deficient diet was 5.42 n moles/mg protein, which was significantly ($p<0.01$) lower value than that of normal diet group with 6.33 n moles/mg protein. When ginseng ethanol extract or ginseng total saponin was administered to the rats fed potassium deficient diet, the sialic acid contents were 6.11 n moles/mg protein and 5.91 n moles/mg protein, respectively. Those values were similar to normal value and significantly ($p<0.05$) higher than that of potassium deficient diet treated group (Table IV).

Table IV. Sialic acid concentrations of heart sarcolemmal ghost preparations.

Rats	No. of experiments[a]	Sialic acid concentration (nmol/mg. protein)
Normal diet	5	6.33±0.12
K-deficient diet	5	5.42±0.11***
K-deficient diet+Ginseng ethanol extract	6	6.11±0.18
K-deficient diet+Ginseng total saponin	5	5.91±0.17

Data are given as Means±S.E.
a; Each experiment was performed with pooled preparation from 5~10 rats.
Significantly different from control; ***$p<0.001$

Table V. Effect of orally administered ginseng ethanol extract (100mg/kg) or ginseng total saponin (50mg/kg) on the sialyltransferase activity of cardiac ventricular tissue from potassium depleted rats.

Rats	No. of experiments[a]	Sialyltransferase activity (pmol/mg. protein/hr.)
Normal diet	11	4.10±0.21
K-deficient diet	13	3.13±0.18**
K-deficient diet+Ginseng ethanol extract	10	3.79±0.17
K-deficient diet+Ginseng total saponin	4	2.89±0.27**

Data are given as Means±S.E.
a; Each experiment was performed with pooled preparation from 5~10 rats.
Significantly different from control; **$p<0.01$

Sialyltransferase Activities

The sialyltransferase activities of the sarcolemma and various subcellular fractions from heart ventricular tissue of normal rats were determined. The sialyltransferase activity of 40,000×g pellet had the highest value, so the 40,000×g pellets were prepared from all the experimental groups and their sialyltransferase activities were compared.

Sialyltransferase activities of potassium deficient diet fed group was 3.13 p moles/mg protein/hr, which was significantly ($p<0.01$) lower than normal diet group with the enzyme activity of 4.10 p moles/mg protein/hr. When ginseng ethanol extract was administered to to the rats fed potassium defficient diet, sialyltransferase activity was 3.79 p moles/mg protein/hr, which was significantly ($p<0.05$) higher than potassium deficient diet fed group. In ginseng total saponin treated group, however, such tendency was not observed (Table V).

Calcium Uptake by S.R. preparations

Calcium uptake by SR was 497.8 nmoles/mg protein in potassium depleted myocardium after 20 minutes incubation, and 362.3 n moles/mg protein in normal diet group at the same duration. The difference was significant ($p<0.05$).

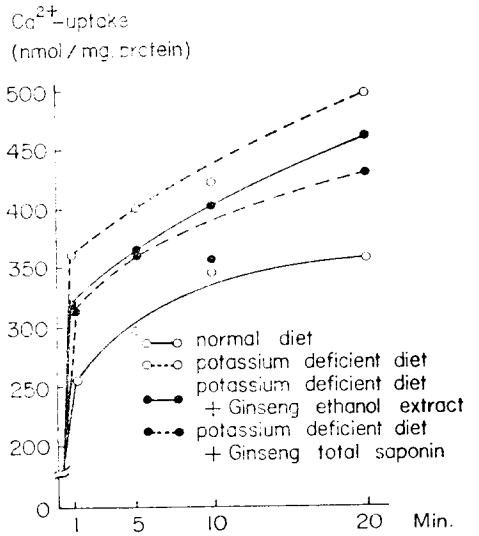

Fig. 3. Ca^{2+}-uptake by heart sarcoplasmic reticulum prepared from control and treated rats.

SR calcium uptake in ginseng components treated groups had a tendency to be increased from normal value but not so high as in potassium depleted myocardium (Fig. 3).

DISCUSSION

The present study was performed to investigate the effects of ginseng components on the potassium depletion induced cardiomyopathic rat, which is one of the well-known pathological animal models, used in heart research.[17,18,19,20,21,22]

When the potassium deficient diet was supplied to the rats from 6 week-old age, the growth curve was retarded compared to normal diet group. Similar results were presented by Naito *et al.*[23]. Although ginseng ethanol extract or ginseng total saponin was administered for 2 weeks concurrently with the potassium deficient diet, the retardation of growth in potassium deficient group was not reversed. Thus ginseng components were found not to act as potassium sources.

Many investigators[24,25,26] reported that serum potassium concentration was decreased in potassium depleted state, whereas potassium concentration in cardiac muscle was not. Similar results are observed in our experiment. The serum potassium concentration was not decreased in the potassium deficient diet group which concurrently treated with ginseng components. This result suggests the possibility of ginseng components to increase potassium saving effect on potassium depleted states.

Kim *et al.*[3] reported the contractile force of isolated hearts from ginseng treated rats deteriorated slower than that of normal rats and similar results are presented by Toh *et*

al.[27] In this experiment, ginseng components show the ability to delay the deterioration rate of contractile force also in the potassium depleted cardiomyopathic rat hearts. This fact suggests that ginseng components have a protecting action against the progress of potassium depleted cardiomyopathy in rats.

Sialic acid is preferentially localized on the plasma membrane as a terminal saccharide of glycoproteins since as much as 65~70% of the total cellular content is associated with cell surface structures.[28] It was demonstrated that removal of sialic acid from cardiac cell surface by neuraminidase treatment increased cellular permeability to calcium.[28,29] Therefore many investigators regarded the sialic acid as a putative binding site for calcium ion.[30]

In the present study, sialic acid content in the sarcolemmal ghost prepared from heart ventricular muscle of potassium depleted rats was significantly lower than that of normal diet group. This indicates that abnormal condition of calcium transport caused by the decrease of sialic acid content in sarcolemmal glycoprotein is one of the possible reasons for the induction of potassium depleted cardiomyopathy.

Sialyltransferase (CMP-N-acetyl neuraminate; D-galactosyl glycoprotein, N-acetylneuraminyl transferase, EC 2.4.9.1.) is distributed all over the body tissue, especially in blood cell rane,[31] tumor cell membrane,[14,32,33] skeletal memb muscle plasma membrane,[21] and subcellular fractions such as golgi complex[34,35,36] and microsomal fraction.[12]

In our experiment, sialyltransferase activity was not found in sarcolemmal ghost preparation, but in 40,000×g pellet among subcellular fractions which might contain golgi complex and heavy microsomal fraction. Sialyltransferase activity of that subcellular fraction prepared from heart venticular tissue of potassium depleted rats was significantly lower than tha tof normal diet group. Decrease of sialic acid content in sarcolemmal preparation, therefore, seems to be related with the decrease of sialyltransferase activity.

Such decreasing tendency in sialic acid content and sialyltransferase activity was diminished when ginseng ethanol extract was administered together with the potassium deficient diet. Accordingly it is suggested that ginseng has the ability to help the calcium transport function of sarcolemma by preventing the decrease of sialyltransferase activity and thereby maintaining the integrity of sialic acid linked glycoprotein in sarcolemma.

There have been many reports on calcium uptake or release by SR in connection with E-C coupling. When there exist a cardiac malfunction such as cardiomyopathy or cardiac hypertrophy, calcium uptake capacity by SR prepared from the ventricular muscle was reported to be lower than normal animal [Kim *et al.*[19] and Harigaya *et al.*,[15] whereas opposite results were presented by Kahlon *et al.*[37] and Malhota.[38] On the other hand, Dhalla and coworkers[6] reported that calcium binding (in the absence of oxalate) ability of SR isolated from failing hearts of genetically dystrophic hamsters (BID 14.6 strain) was decreased, while calcium uptake (in the presence of oxalate) ability was similar to that of the control heart. Boegman *et al.*[39] also found that SR calcium binding was remarkably decreased, while calcium uptake was rather increased in the batrachotoxin treated animals.

In this study, SR calcium uptake was increased in the potassium depleted rats compared with normal diet group. Considering these results in connection with the decrease of sialic acid content in sarcolemma, the incresed calcium uptake might be predicted as a compensatory effect to take up the amount of calcium which

permeated into the cytoplasm due to malfunction of sarcolemma. These results are in disagreement with afore-mentioned reports by some investigators and further study is needed to clarify this aspect.

The SR calcium uptake in the rats administered ginseng ethanol extract with potassium deficient diet, was increased compared to the normal diet group, but was lower than that in the potassium depleted rats. This result suggests the possible protecting effect of ginseng components against the advance of potassium depleted cardiomyopathy, although it is not clear at present whether it is secondary to the primary effect of ginseng components on SR.

For the effect of ginseng components on SR calcium uptake, Lee[40] and Kim *et al.*[41] suggested that ginseng components decrease the SR calcium uptake. Their results are similar to ours, but the direct comparison may need caution in view of the different methods used by these authors.

In summary, this study suggests that ginseng components have a protecting action against the progress of potassium depletion-induced cardiomyopathy in rats through the possible mechanism of preventing the decrease of sialyltransferase activity in cardiac muscle cell and sialic acid content in sarcolemma.

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