Effect of Panax Ginseng Alcohol Extract on Cardiovascular System

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The effects of the alcohol extract of Panax ginseng on the myocardial contractility particularly with respect to Bowditch and Woodworth phenomena and the norepinephrine induced contraction of the vascular smooth muscle were studied in vitro.

1) In the isolated muscle preparation of guinea pig left auricle, the administration of ginseng-alcohol extract at concentrations of 10~50 mg% resulted in a significant reduction of both Bowditch and Woodworth effects.

2) In the isolated Ca++ depleted heart of rabbit ginseng-alcohol extract inhibited the Ca++ uptake and the restoration of contractile force during perfusion with a Ca++ containing solution.

3) In the isolated muscle strip of the rabbit aorta noradrenaline (5×10^-8 g/ml) induced contraction was inhibited by the ginseng-alcohol extract at concentrations of 10~50 mg%.

From these results it is speculated that the hypotensive effect of ginseng is accounted for by 1) the direct inhibition of myocardial contractility which is resulted from the reduction of Ca++ influx into cardiac cell, and 2) the inhibition of the catecholamine induced contractility of vascular smooth muscles.

Various types of pharmacological studies on the biological effect of ginseng root have been conducted in the past by a number of investigators (Petkov, 1961; Kitagawa and Iwaki, 1963; Wood et al., 1964; Lim, 1967; Brekhmann 1969; Takagi et al., 1972a~1972b; Nabata et al., 1973). For instance, Petkov (1961) has observed that ginseng root stimulates the functions of the central nervous system, the respiration and the adrenal cortex.

It was also reported that ginseng root stimulates gastric and intestinal motilities (Yoon, 1960), corrects nutritional disorders and depresses mean arterial blood pressure (Hwang, 1960). The cardiovascular effect of ginseng has been further documented by other investigators. Kitagawa and Iwaki (1963) reported that the injection of alcohol extract of Panax-ginseng to the dog reduces blood pressure but has no apparent depression of cardiac contractility. Wood et al., (1964) have found a transitory hypotension after an intravenous injection of alcohol extract of ginseng which was promptly followed by a more prolonged

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hypertension. From these they speculated that ginseng has an effect specifically on the vascular system.

In the present study, we have attempted to investigate the mechanism of ginseng effect on the cardiovascular system. The direct effect of ginseng on the myocardial contractility particularly with respect to Bowditch and Woodworth staircase phenomena was first studied, and then the effect of ginseng on norepinephrine induced contractility of isolated vascular smooth muscle was investigated.

MATERIALS AND METHODS

I. Effect of ginseng on the Bowditch and Woodworth staircase phenomena

In the first series of experiments the effect of ginseng on the Bowditch and Woodworth staircase phenomena was examined using guinea pig left auricular muscle strips by the method of Hajdu (1969). A guinea pig weighing 200–300 g was stunned by a blow on the head, and then the thorax was opened quickly. The heart was taken out and transferred into cold Krebs-Henseleit solution which consisted of NaCl 140 mM, KCl 4.7 mM, KH₂PO₄ 1.2 mM, MgSO₄ 2.4 mM, NaHCO₃ 23 mM, glucose 10 mM, and CaCl₂ 2 mM. The left auricular muscle was dissected into small strips of 2 mm in width and about 6–7 mm in length. They were then suspended in a organ bath (Fig. 1) containing Krebs-Henseleit solution which had been gassed with 95% O₂–5% CO₂.

One end of a strip was tied to the bottom of the incubation bath and the other end was connected to a force transducer (Grass Model FT03C) to record tension on a polygraph.

The pH of the bathing solution was adjusted to 7.35±0.05 and temperature was maintained at 37°C. The tension was recorded when the strip was stimulated through a platinum wire with a supramaximal strength and 2 msec duration at varying intervals of 0.2, 0.5, 1, 2, 5, 10, 30, 60, 120, and 180 sec. After the normal interval tension relationship was established ginseng alcohol extract was added to the bathing medium and tension was recorded again as before.

II. Effect of ginseng on the Ca²⁺ uptake and the restoration of contractile force in the Ca²⁺ depleted rabbit ventricle

In the isolated, perfused and Ca²⁺ depleted rabbit ventricle prepared by the method of Bailey and Dressel (1968), the effects of ginseng on the Ca²⁺ uptake and the contractile force were studied.

Rabbits of either sex, weighing 1.5–2 Kg were sacrificed, the thorax was opened rapidly and the heart was totally excised. After all extraneous tissues and both auricles were removed a cannula was inserted into aorta and held by a ligature around aorta. And then a small incision was made on the apex
of each ventricle so that perfusate through coronary vessels could drain freely from the apex.

The cannulated heart was attached securely to the perfusion apparatus and a stainless steel fish-hook was firmly attached to the apex. The heart preparation was transferred in a air-filled and double-walled glass chamber. The temperature in the chamber was maintained at 37°C by circulating warm water through the double wall. The pressure of the perfusate of the heart was adjusted to 122 cm H₂O. A length of nylon thread connected the fish-hook through a small hole to a force transducer outside the chamber as shown schematically in Fig. 2. The preparation was perfused first with normal Krebs-Henseleit solution gassed with a warmed, water-saturated mixture of 95% O₂-5% CO₂. The stimulating electrodes were attached to the ventricular muscle and the heart was stimulated with a twice threshold voltage at a frequency of 180/min throughout the experiment using a Grass SD5 stimulator. Resting tension was maintained at 10 g throughout the experimental periods. Isometric tension was recorded on a Grass 7 polygraph. The perfusate used in these series of experiments was Krebs-Henseleit solution containing NaCl 118.0 mM, KCl 4.7 mM, KH₂PO₄ 1.2 mM, MgSO₄ 2.4 mM, NaHCO₃ 25.0 mM, glucose 10.0 mM, and CaCl₂ 0 or 2 mM. The preparations were initially perfused with the normal Krebs-Henseleit solution containing 2 mM of CaCl₂. After 4 min preperfusion with the above solution, the perfusate was switched to Ca²⁺ free Krebs-Henseleit solution. At this time the contractile force decreased to near zero. In order to see the relationship between Ca²⁺ uptake and restoration of contractile force of this Ca²⁺ depleted ventricle, a serial sample of effluent for 10 sec from the heart was collected until the contractile force was restored completely or to steady level after reperfusion with the normal (Ca²⁺ containing) Krebs-Henseleit solution. The concentrations of Ca²⁺ of the samples were determined by the method of Mager and Farese (1966).

III. Effect of ginseng alcohol extract on the norepinephrine induced contraction of isolated rabbit atrial muscle

Rabbit of either sex, weighing 1.5~2.5 Kg were killed by a blow on the head and then bled. The thorax was opened and the heart with aorta was taken out. The entire descending aorta was quickly but gently excised, and adherent fat and loose connective tissues were removed. The longitudinal or circumferential strips of vascular wall with 1.0 to 1.5 mm in width and about 5.0 to 6.0 mm in length were made. These preparations were suspended in an organ bath containing Krebs-Henseleit solution which had been gassed with 95% O₂-5% CO₂. One end of a strip was then tied to the bottom of the incubation vessel and the other end was connected to a force transducer to record tension on a poly-
The pH of the bathing solution was adjusted to 7.25±0.05 and temperature was maintained at 37°C. Since spontaneous contraction of the muscle was not usually seen, the contraction was induced by adding a small amount of norepinephrine (5×10^{-6} g/ml) to the medium. When the induced contraction showed a steady level, the ginseng extract was added to the bathing medium and changes in contractility was followed.

The ginseng alcohol extract was prepared by the following procedure. The root of Panax ginseng (from Keumsan, Korea) was ground and extracted for about 300 hrs with boiling absolute ethanol in a distilling apparatus with water cooled reflux condenser, and water bath for the distiller was maintained at 80°C.

Ethanol in the extract was subsequently evaporated to a sticky residue and the residue was kept in a desiccator in cold room until the use. An aliquot of the residue was dissolved in Krebs-Henseleit solution to obtain appropriate concentrations.

**RESULT**

**I. Effect of Panax-ginseng on Bowditch and Woodworth staircase phenomena**

Both the Bowditch and Woodworth staircase phenomena are readily demonstrable in the auricular muscle of guinea pig. Fig. 3A shows a typical tracing of tension development by the left auricular strip. As is seen, when stimulating frequency was increased from 0.3 pulse/sec (left tracing) to 3 pulse/sec (center tracing) there was a marked increase in the muscle tension, showing a typical Bowditch staircase phenomenon. When the stimulating frequency was decreased back to 0.3 pulse/sec (right tracing) an abrupt but transitory increase in tension was observed. This phenomenon is known as the additive effect of remaining Bowditch and newly developed Woodworth staircase phenomenon. When ginseng was added to the incubation bath at concentrations of 10 (Fig. 3B), 50 (Fig. 3C), and 100 (Fig. 3D) mg% both Bowditch and Woodworth effects were reduced.

Fig. 4 represents steady-state interval-tension relation of guinea pig left auricle.
sion curves in the control and ginseng treated auricular muscle. As is seen, at the stimulus intervals above 2 sec the tension development by the muscle was directly proportional to the interval, whereas at the stimulus interval less than 2 sec it was inversely proportional ginseng effect to the interval, showing a typical Woodworth and Bowditch phenomena respectively.

It should be noted that both Bowditch and Woodworth phenomena were inhibited by the ginseng extract at 20–50 mg%.

II. Effect of Panax-ginseng on the Ca\(^{++}\) uptake and restoration of the contractile force of the isolated perfused heart

Isolated hearts were perfused for 4 min with Krebs-Henseleit solutions containing 2 mM Ca\(^{++}\), and then perfused with Ca\(^{++}\) free Krebs-Henseleit solution to deplete Ca\(^{++}\) from the tissue. As illustrated in Fig. 5A, perfusion with Ca\(^{++}\) free solution resulted in a gradual reduction of contractile force.

When this preparation was perfused with a Ca\(^{++}\) containing medium, however, the contractility was restored. This recovery of contractility was severely impaired in the ginseng treated preparations (Fig. 5B).

In an attempt to establish the underlying mechanism for this finding we next investigated the effect of ginseng on the Ca\(^{++}\) uptake and the contractile force of the Ca\(^{++}\) depleted heart during the recovery period after perfusion with Ca\(^{++}\) containing Krebs-Henseleit solution. Ca\(^{++}\) uptake by the heart was estimated by analyzing the Ca\(^{++}\) concentrat-

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**Fig. 5.** A typical record of changes of the contractility followed by reperfusion of 2 mM Ca\(^{++}\) Krebs-Henseleit solution with or without Panax ginseng after Ca\(^{++}\) depletion.

**Fig. 6.** Effect of Panax ginseng alcohol extract on Ca\(^{++}\) uptake and restoration of contractile force of Ca\(^{++}\) depleted rabbit ventricle after reperfusion with normal Krebs-Henseleit solution.
tions in the aliquots of effluents collected at a 10 sec interval. As shown in Fig. 6, both the initial rate of restoration and steady state level of contractility were significantly lower in the ginseng treated heart than in the control. Similarly, the Ca** uptake by the heart, both initial rate and the steady state tissue concentration, was reduced by ginseng treatment.

III. Effect of Panax-ginseng extract on the contractility of aortic muscle

The contraction of the isolated aortic muscle was induced with noradrenaline. Dose of noradrenaline was adjusted to give a submaximal contraction of the muscle strip.

When the contraction reached a steady plateau state an appropriate concentration of Panax-ginseng was administered to the bathing medium. As illustrated in Fig. 7, the noradrenaline induced contraction was declined after ginseng (10~50 mg%) treatment, the effect being proportional to the dose of ginseng. The contraction induced by 1×10^-6 g/ml noradrenaline was completely removed by 50 mg% of ginseng.

![Figure 7](image)

**Fig. 7.** Effect of Panax ginseng alcohol extract on the noradrenaline induced contraction of descending aortic strip.

DISCUSSION

Effects of the ginseng root extract on the cardiovascular system have been documented by a number of authors (Petkov, 1961; Kitagawa and Iwaki, 1963; Wood et al., 1964; Lim, 1967; Brekhmann, 1969; Takagi et al., 1972a~1972b; Nabata et al., 1973). These include a depression of cardiac function (Hwang, 1960), a reduction in the blood pressure (Kitagawa and Iwaki, 1963), and a transitory hypotension which is followed by a prolonged hypertension (Wood et al., 1964). Although Wood et al. (1964) have proposed that the change in blood pressure by ginseng is produced at the vascular level, overall mechanisms of ginseng effect on the cardiovascular system in general are not fully understood.

In the present studies we have tested the possibility that ginseng affects cardiovascular functions through a direct inhibition of cardiac contractility and an attenuation of vascular contractility induced by noradrenaline. In isolated muscle strips of the guinea pig auricle ginseng inhibited both Bowditch and Woodworth staircase phenomena (see Fig. 3 & 4). The Bowditch staircase phenomenon, an enhanced contractility resulting from rapid successions of contractions by high, stimulating frequency, is thought to be a result of an increased Ca** influx from extracellular fluid (Hagiwara and Nakajima, 1966; Reuter, 1967; Hajdu, 1969), on the other hand Woodworth staircase phenomenon, an increase in contractility at very slow stimulating frequency, may be a result of a larger amount of Ca** release from the intracellular Ca** pools (Hajdu, 1969). The Ca** pool is consisted of sarcoplasmic reticulum (De Caro, 1967; Caldwell, 1968), the inner surface of cellular membrane (Niedergerke, 1957), mitochondria (Washington and Murphy, 1962) and other components of the cell (Langer, 1964; Bailey and Dressel, 1968). The present data, however, do not permit us to distinguish which components of the Ca** pool is primarily affected by ginseng. Recent studies of Kim et al., (1977) and Lim and Choi (1975) indicated that the Ca** uptake by sarcoplasmic reticulum
and mitochondria and Ca++ activated ATPase activities are strongly inhibited by the ginseng alcohol extract. Whether the ginseng has a similar effect in other components of Ca++ pool has yet to be determined.

The present studies provided a strong evidence for the ginseng inhibition of Ca++ influx in the cardiac cell. In the isolated Ca++ depleted heart recovery of tissue Ca++ and contractile force during perfusion with Ca++ containing medium were significantly retarded by ginseng (see Fig. 6). It is therefore apparent that the inhibition of Bowditch staircase phenomenon by ginseng is primarily accounted for by the inhibition of Ca++ influx.

In the studies with isolated aortic strips, noradrenaline induced contraction was inhibited by ginseng (see Fig. 7). The mechanism of this response is not understood at present. Nevertheless, it seems clear that the inhibition of catecholamine response of vascular smooth muscle is in part responsible for the ginseng induced hypotension. A similar conclusion has been drawn by Hwang (1960) in his studies on cats and rabbits. It would be therefore valuable to study the effect of ginseng in the vascular muscle treated with adrenergic blocking agents.

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