

Influence of Total Ginseng Saponin on Contractile Responses of Vasoconstrictors in the Isolated Rat Aorta

Choon-Hae Chung, MD¹, Soon-Pyo Hong, MD¹, Seong-Ho Cho, MD²,
Jang-Gwon Hong, MD², Yong-Kyoon Lee, MD², Geon-Han Lim, MD²,
Won-Ho Yang, MD², Ho-Jin You, MD², Seong-Chang Woo, MD²,
Cheol-Hee Choi, MD² and Dong-Yoon Lim², PhD

¹Department of Internal Medicine and ²Pharmacology, College of Medicine, Chosun University, Kwangju, Korea

흰쥐 대동맥에서 총인삼사포닌이 혈관수축제의 수축반응에 미치는 영향

정춘해¹ · 홍순표¹ · 홍장권² · 조성호² · 이용균² · 임건한²
양원호² · 우성창² · 유호진² · 최철희² · 임동윤²

국문 초록

연구배경 :

가 .

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isometric force transducer Physiograph
. 결 과 : Phenylephrine())
(600 µg/ml) phen -
ylephrine(10^{-5} 10^{-6} M) (3.5×10^{-2} 5.6×10^{-2} M)
prostaglandin F₂ (5×10^{-6} M) . Phen -
ylephrine(10^{-5} M) (3.5×10^{-2} M) (600 µg/ml)
calcium channel blocker nifedipine(10^{-6} M) . 결 론 :
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중심 단어 :

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Corresponding author : Dong-Yoon Lim, 375 Seosuk-Dong, Dong-Gu, Kwangju 501-759, Korea
Department of Pharmacology, College of Medicine, Chosun University, Kwangju 501-759, Korea
TEL : (062) 220-3659 · Fax : (062) 227-4693
E-mail : dylim@mail.chosun.ac.kr.

Introduction

It has been shown that total Ginseng saponin produces the pressor and depressor actions in the anesthetized normotensive rats.¹⁾ It has suggested that this depressor response is mediated in part through the blockade of adrenergic α -receptors as well as the stimulation of cholinergic muscarinic receptors, and that its pressor response is caused by stimulation of nicotinic cholinergic receptors at the sympathetic ganglia. Furthermore, Choi²⁾ has reported that total Ginseng saponin can inhibit the releasing effect of catecholamines evoked by nicotinic receptor stimulation from the isolated perfused rat adrenal medulla, which seems to be associated to the direct inhibition of calcium influx into the rat adrenomedullary chromaffin cells. In the isolated perfused rat adrenal glands, total Ginseng saponin increases a calcium-dependent secretion of catecholamines via direct action on chromaffin cells with partly mediation of muscarinic action.³⁾

In previous studies, it has been known that Ginseng extract causes the hypotensive action⁴⁻⁸⁾ while it rather produces the hypertensive action.⁹⁻¹⁰⁾ Some studies have suggested that Ginseng extract causes a biphasic response on blood pressure, namely, transient fall followed by prolonged elevation.¹¹⁻¹³⁾ Furthermore, Ginseng, when given at small dose in spontaneously hypertensive rat (SHR), cause pressor response, but at relatively large dose rather produces dose-dependent hypotensive response with decreased plasma renin activity.¹⁴⁻¹⁶⁾ Sokabe and his coworkers¹⁷⁾ have shown that administration of Korean Red Ginseng powder for 11 weeks has no effect on blood pressure in normotensive Donryu (DON) rats, SHR and renal hypertensive rats, whereas it elevates slightly blood pressure in deoxycorticosterone salt hypertensive rats.

Lim and his coworkers¹⁸⁻¹⁹⁾ have also found that both of panaxadiol- and panaxatriol-type saponins cause the increased secretion of catecholamines (CA) in a Ca^{2+} -dependent fashion from the isolated perfused rabbit adrenal glands through the activation of cholinergic (both nicotinic and muscarinic) receptors and partly the direct action on the rabbit adreno-medullary chromaffin

cells. As mentioned so far, there are many controversial reports on vascular effects of Ginseng saponin.

Therefore, the present study was attempted to examine the effect of total Ginseng saponin on contractile responses evoked by stimulation of adrenergic α_1 -receptors and membrane depolarization in the isolated rat aorta and to clarify the mechanism of its action.

Materials and Methods

Experimental procedure

Mature male Sprague-Dawley rats, weighing 150 to 350 grams, were used in the experiment. The animals were housed individually in separate cages, and food (Cheil Animal Chow) and tap water were allowed ad libitum for at least a week to adapt to experimental circumstances. On the day of experiment, a rat was anesthetized with thiopental sodium (40 mg/kg) intraperitoneally, and tied in supine position on fixing panel. The thorax was opened by a midline incision, and the heart and surrounding area were exposed by placing three hook retractors. The heart and portion of the lung were not removed, but pushed over to the right side and covered by saline-soaked gauge pads in order to obtain enough working space for isolating aortic vessel. The aorta was isolated from the proximal part of the heart to the vicinity of liver and immediately immersed in cold Krebs solution. The blood within the aorta was rapidly removed. The aorta was cut into the ring of 4 - 5 mm length.

Recording of mechanical activity

The ring segment of aorta was mounted in a muscle bath by sliding the ring over two parallel stainless-steel hook (0.15 mm in diameter). The lower hook was fixed on bottom of the bath and the upper was connected to isometric transducer (Grass FT. 03). The signal from the transducer was displayed on a polygraph (Grass Instruments Model 79). The volume of bath was 25 ml and the bath solution was saturated with 95% O_2 and 5% CO_2 at 37 °C.

The composition (mM) of Krebs was : NaCl, 118.4 ; KCl, 4.7 ; $CaCl_2$, 2.5 ; $MgCl_2$, 1.18 ; $NaHCO_3$, 25 ; KH_2PO_4 , 1.2 ; glucose, 11.7. The final pH of the solution

ion was maintained at 7.4 – 7.5. During equilibration period of 2 hours, the resting tension was adjusted to 0.5 g. After the equilibration period, the ring was challenged with 35 mM KCl two times, and if it responded with contraction, the proper experiment was started. Vasoconstrictors were administered into the bath in order to obtain dose-response curves. In the subsequent experiments, under the presence of total *Ginseng* saponin some vasoconstrictors were administered. The data were expressed as % of the control tension.

Statistical analysis

The statistical significance between groups was determined by the Student's t-test. A P-value of less than 0.05 was considered to represent statistically significant changes unless specifically noted in the text. Values given in the text refer to means and the standard errors of the mean (S.E.M.). The statistical analysis of the experimental results was made by computer program described by Tallarida and Murray.²⁰⁾

Drugs and their sources

The following drugs were used : phenylephrine hydrochloride, prostaglandin F₂ tris salt, potassium chloride and nicardipine hydrochloride (Sigma Chemical Co., U. S. A.). Total *Ginseng* saponin was a gift from late Dr. Young-Ho Kim (Sejong University, Seoul, Korea). Drugs were dissolved in distilled water (stock) and added to the normal Krebs solution as required. Concentrations of all drugs used are expressed in terms of molar base except Total *Ginseng* saponin (g/ml).

Results

The effects of total *Ginseng* saponin on contractile responses induced by phenylephrine, high K⁺ and prostaglandin F₂ in the isolated rat aortic strips

The resting (basal) tension from the isolated rat aortic strips reaches a steady state after the perfusion with oxygenated Krebs-bicarbonate solution for 90 min before the experimental protocol is initiated. The resting tension was adjusted to 0.5 g. The effects of total *Ginseng* saponin on phenylephrine- as well as potassium chloride-mediated contractile responses in the rat

aorta were examined. In the present study, total *Ginseng* saponin itself did not produce any effect on the resting tension (data not shown).

When 10⁻⁶ M and 10⁻⁵ M of phenylephrine were administered into the aortic bath, the active tensions of them were 0.75 ± 0.05 g and 1.02 ± 0.12 g from the resting tension level, respectively. However, under the preloading with total *Ginseng* saponin at a concentration of 600 µg/ml, phenylephrine-induced tensions were significantly potentiated to 1.14 ± 0.11 g (p < 0.01) and 1.52 ± 0.13 g (p < 0.01) from resting level from 7 rat aortic strips, which were 152.0% and 149.1% of the control contractile responses, respectively, as shown in Figs. 1 and 2.

High K exerts two distinct effects on cells : (1) depolarization of cell membrane, and (2) depolarization-induced influx of calcium via voltage-dependent calcium channels.²¹⁾

When added through the bath, high potassium at the concentration of 35 mM and 56 mM, which is mem-

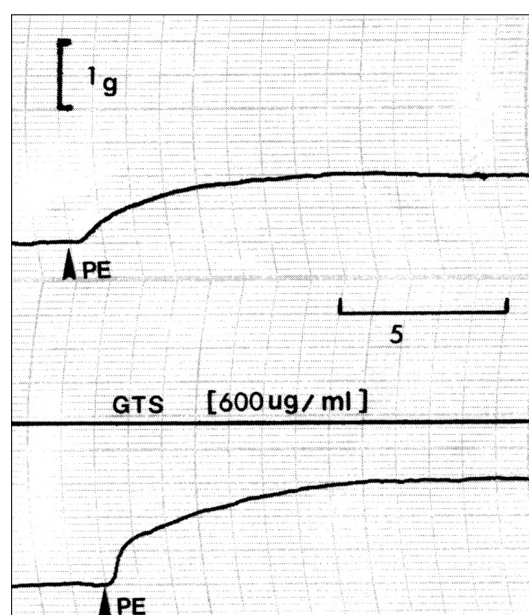


Fig. 1. The typical tracing showing the effect of total *Ginseng* saponin (GTS) on phenylephrine (PE)-induced contractile responses in the rat aortic strip. Upper : PE-induced contractile response. Lower : PE-induced contractile response in the presence of total *Ginseng* saponin (600 µg/ml). At arrow mark, the indicated dose (10⁻⁵ M) of phenylephrine was added to the bath. The chart speed was 5 mm/min.

brane depolarizing agent, caused an increase in aortic contraction, respectively. As shown in Fig. 3 and 4, high potassium-induced contractile responses before preloading with total Ginseng saponin were 1.13 ± 0.19 g and 1.58 ± 0.17 g, while after pretreatment with total Ginseng saponin at a concentration of $600 \mu\text{g/ml}$ they were greatly enhanced to 1.56 ± 0.18 g ($p < 0.01$) and 2.27 ± 0.21 g ($p < 0.01$), which were 138.1% and 143.7% of the corresponding control from 8 rat aortic strips, respectively.

Since it has been found that prostaglandin F_2 (5×10^{-6} M) is a vasoconstrictor in dog cerebral arteries²²⁾, it is likely interesting to examine the effect of total

traction in the rat aortic strips. Prostaglandin F_2 (5×10^{-6} M) produced prominent and steady-state contraction in the rat aortic strips as shown in Fig. 5. In 6 rat aortic strips, prostaglandin F_2 (5×10^{-6} M) caused the contractile response of 1.32 ± 0.18 g from the resting tension level but, even in the presence of total Ginseng saponin ($600 \mu\text{g/ml}$), it was not affected (98.5% of the control) as in Fig. 6.

The effect of nicardipine on total Ginseng saponin-induced potentiation of the contractile response evoked by high K^+ in the isolated rat aorta

In order to investigate the effect of nicardipine, a dihydropyridine derivative and L-type Ca^{2+} channel blocker²³⁾ on total Ginseng saponin-induced potentiation of the contractile response evoked by high potassium in the rat aortic strips, nicardipine (10^{-6} M) was preloaded into the bath. In the presence of nicardipine effect, total Ginseng saponin-induced potentiation of the contractile response evoked by high potassium (35

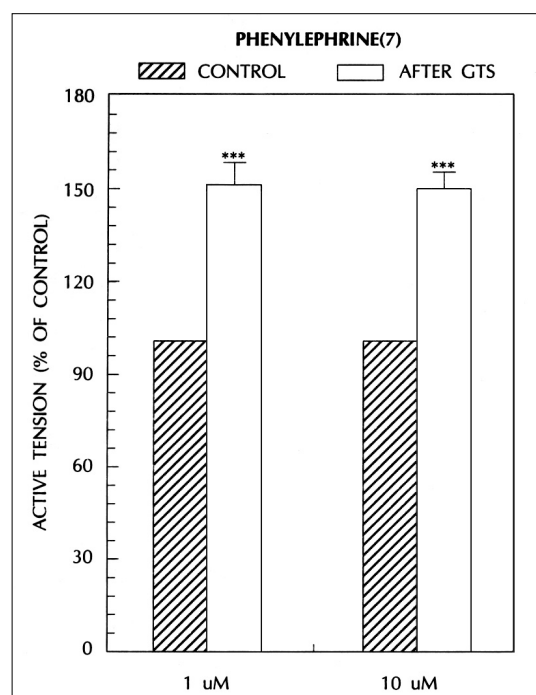


Fig. 2. Influence of total Ginseng saponin (GTS) on phenylephrine (PE)-induced contractile responses in the isolated rat aortic strips. The contractile response was induced by adding 1 uM and 10 uM of PE, respectively after adaptation with normal Krebs solution for two hours prior to initiation of the experimental protocol. "CONTROL" and "AFTER" denote active tension induced evoked by PE before (CONTROL) and after adding total ginseng saponin ($600 \mu\text{g/ml}$), respectively. Number in the parenthesis indicates number of experimental rat aortic strips. Vertical bars represent the standard error of the mean (S.E.M). Ordinate: the active tension (% of control). Abscissa: concentrations of PE (M). Statistical difference was obtained by comparing the control with the GTS-pretreated group. ***: $p < 0.01$

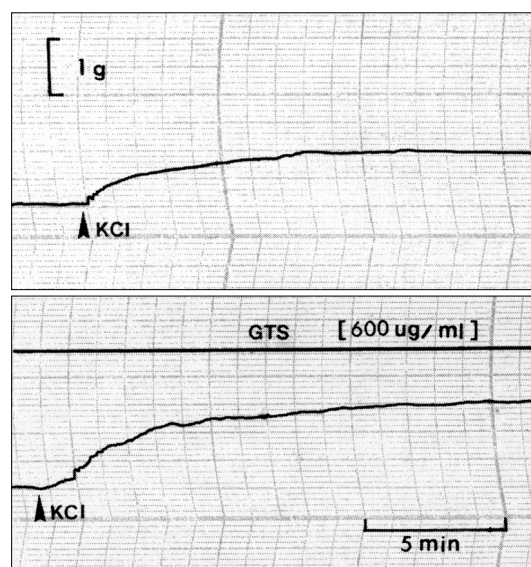


Fig. 3. The typical tracing showing the effect of total Ginseng saponin (GTS) on high potassium (KCL)-induced contractile response in the rat aortic strip. Upper: KCL-induced contractile responses. Lower: KCL-induced contractile response in the presence of total Ginseng saponin ($600 \mu\text{g/ml}$). At dots, the indicated doses (35 mM) of KCL was added to the bath. The chart speed was 5 mm/min.

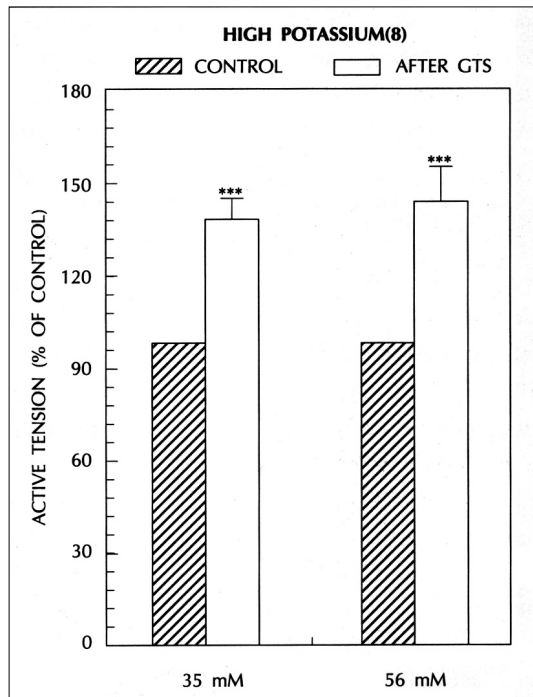


Fig. 4. Influence of total Ginseng saponin (GTS) on high potassium-induced contractile responses in the isolated rat aortic strips. High potassium (35 and 56 mM, respectively) was added into the bath before and after pretreatment with GTS (600 μ g/ml). Other legends are the same as in Fig. 2. *** : $p < 0.01$

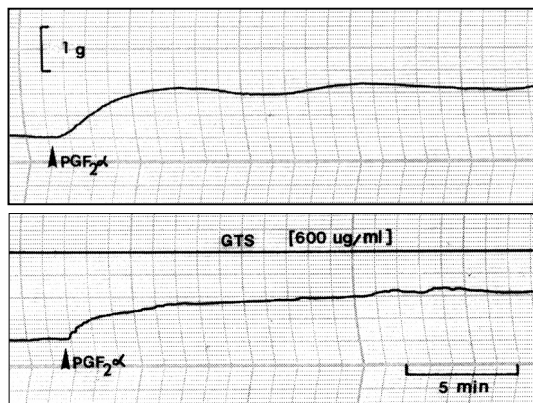


Fig. 5. The typical tracing showing the effect of total Ginseng saponin (GTS) on prostaglandine $F_{2\alpha}$ ($PGF_{2\alpha}$)-induced contractile responses in the rat aortic strip. Upper : $PGF_{2\alpha}$ -induced contractile response. Lower : $PGF_{2\alpha}$ -induced contractile response in the presence of total Ginseng saponin (600 μ g/ml). At dots, the indicated dose (5×10^{-6} M) of phenylephrine was added to the bath. The chart speed was 5 mm/min.

mM) were greatly depressed to 0.31 ± 0.02 g (19.4% of the control, $p < 0.01$) from the resting tension level from 6 adrenal glands in comparison with their corresponding control values of 1.60 ± 0.15 g as depicted in Fig. 7 and 8.

Discussion

The present experimental results suggest that total Ginseng saponin potentiates the contractile responses induced by stimulation of adrenergic α_1 -receptor and the membrane depolarization in the isolated rat aortic strips, which appears to be in relation to calcium influx.

Generally, extracellular Ca^{2+} has been unequivocally shown to play a critical role in excitation-contraction coupling in vascular smooth muscle. Most of cellular mechanisms accepted in accounting for the contraction of vascular smooth muscle by various agents are based on increased intracellular Ca^{2+} either through influx of extracellular Ca^{2+} or through release

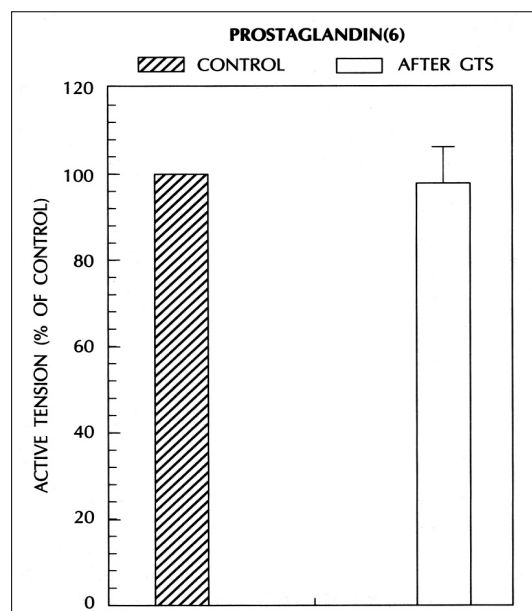


Fig. 6. Influence of total Ginseng (GTS) saponin on prostaglandin F_2 -induced contractile response in the isolated rat aortic strips. prostaglandin F_2 (5 M) was added into the bath before and after pretreatment with GTS (600 μ g/ml). Other legends are the same as in Fig. 2. ns : nonsignificance.

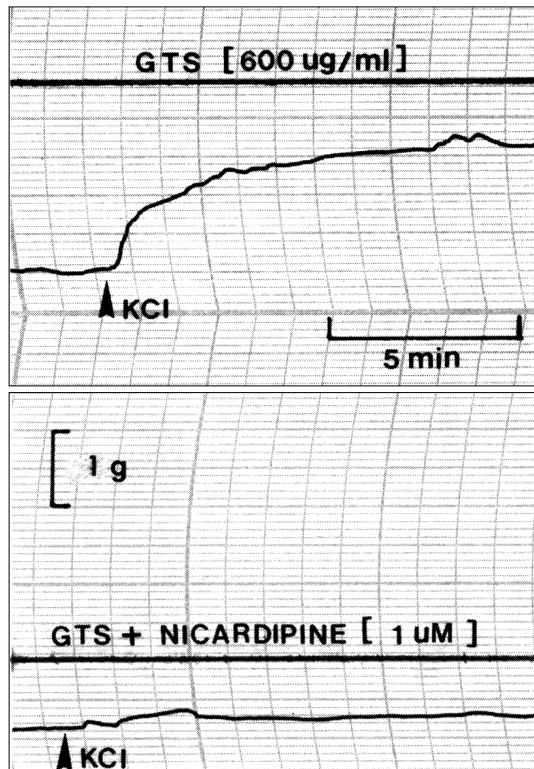


Fig. 7. The typical tracing showing nicardipine effect on potentiation of total Ginseng saponin (GTS) to high potassium (KCl)-induced contractile responses in the rat aortic strip. Upper : the potentiation of GTS (600 μ g/ml) to high potassium-induced contractile response. Lower : nicardipine effect on the potentiation of GTS to high potassium-induced contractile response. At arrow mark, the indicated dose (35 mM) of KCL was added to the bath. The chart speed was 5 mm/min.

of intracellularly stored Ca^{2+} .²⁴⁻²⁷⁾ And it well known that potassium chloride (KCl) opens voltage-dependent calcium channels by depolarizing the cell membrane of vascular smooth muscle, resulting in increased influx of extracellular Ca^{2+} .²⁶⁾²⁸⁻³⁰⁾ Kim and his colleagues³¹⁾ have shown that the contractile responses of vascular smooth muscle induced by CaCl_2 and KCl may result most likely from increased influx of extracellular Ca^{2+} through the voltage-dependent calcium channels. In terms of these results, the present findings that total Ginseng saponin enhances the contraction of rat aortic smooth muscle evoked by phenylephrine (α_1 -adrenergic receptor agonist) and KCl (membrane depolarizer) suggest strongly that total Ginseng saponin can

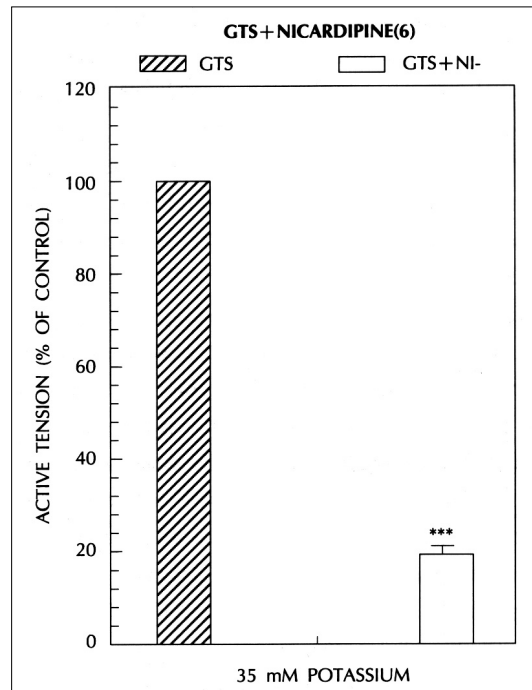


Fig. 8. Influence of nicardipine on total Ginseng saponin (GTS)-induced potentiation of contractile response by high potassium in the isolated rat aortic strips. High potassium (35 mM) along with GTS (600 μ g/ml) was added into the bath before and after pretreatment with nicardipine (1 M). GTS NI : GTSN : cardipine. Other legends are the same as in Fig. 2. *** : $p < 0.01$

facilitate influx of extracellular Ca^{2+} .

In previous studies, three cellular mechanisms have been proposed to explain relaxant response of vascular smooth muscle : (i) blockade of extracellular Ca^{2+} entry into cells,³²⁻³³⁾ (ii) increase in binding or sequestration of intracellular Ca^{2+} ,³⁴⁻³⁵⁾ and (iii) inhibiting the release of intracellular stored Ca^{2+} .³⁵⁻³⁷⁾ In the light of these findings, the present result suggests that total Ginseng saponin can enhance the contractile responses of vascular smooth muscle evoked by phenylephrine and /or KCl through increased extracellular Ca^{2+} entry into the muscle cells. Because the pretreatment with 5 M nicardipine, an inhibitor of the dihydropyridine Ca^{2+} channel, abolished almost completely total Ginseng saponin-induced potentiation of contraction evoked by KCl in the present study.

Moreover, this effect of total Ginseng saponin seems

to contribute at least partly to the facts that Ginseng extract causes the hypertensive action⁹⁻¹⁰⁾, but not to the facts that it rather produces the hypotensive action.⁴⁻⁸⁾ The contractions of vascular smooth muscles induced by neurohumoral agents have been composed of two components : Phasic contraction induced by the Ca^{2+} released from inside the cell and tonic tension related to the Ca^{2+} influx,³¹⁾³⁸⁾ both leading to increased intracellular calcium.

In the present study, prostaglandin F_2 , which is known as a vasoconstrictor in cerebral arteries of the dog²²⁾ and the pig³⁹⁾, caused a contractile response in the isolated rat aortic smooth muscles. However, prostaglandin F_2 -induced contractile response was never influenced by the pretreatment with total Ginseng saponin. This finding indicates that total Ginseng saponin does not affect prostaglandin receptors. Responses to prostaglandin F_2 vary with species and vascular bed. It is a potent constrictor of both pulmonary arteries and veins in human beings.⁴⁰⁻⁴¹⁾

Thus, the most plausible explanation accounting for the facilitatory action of total Ginseng saponin on the vascular contractions induced by stimulation of adrenergic α_1 -receptors and the membrane depolarization in the isolated rat aortic strips is the increased extracellular calcium into muscle cells likewise in neuronal tissues.

Summary

Background :

It has been known that Ginseng extract causes the hypotensive action while it rather produces the hypertensive action. Some studies have suggested that Ginseng extract causes a biphasic response on blood pressure, namely, transient fall followed by prolonged elevation. It has been also shown that administration of Korean Red Ginseng powder has no effect on blood pressure in normotensive and hypertensive rats. The present study was designed to examine the effect of total Ginseng saponin on contractile responses of vasoconstrictors in the rat aorta and to establish the mechanism of its action.

Methods :

The ring segment of aorta was mounted in a muscle

bath filled with oxygenated Krebs solution for the measurement of isometric tension. After the equilibration period, under the presence of total Ginseng saponin, isometric tension induced by some vasoconstrictors were observed and compared to the control responses. The data were expressed as % of the control tension.

Results :

Phenylephrine (an adrenergic α_1 -receptor agonist) and high potassium (a membrane depolarizing agent) caused greatly contractile responses in the rat aorta, respectively. However, in the presence of total Ginseng saponin (600 g/ml), the contractile responses of phenylephrine (10^{-6} and 10^{-5} M) and high potassium (3.5×10^{-2} and 5.6×10^{-2} M) were markedly potentiated whereas prostaglandin F_2 (5×10^{-6} M)-induced contractile responses was not affected. The contractile responses induced by phenylephrine (10^{-5} M) and high potassium (3.5×10^{-2} M) even under the presence of total Ginseng saponin (600 g/ml) were greatly inhibited by the pretreatment of nicardipine (10^{-6} M), a calcium channel blocker.

Conclusion :

Taken together, these experimental results suggest that total Ginseng saponin can enhance the contractile responses evoked by stimulation of adrenergic α_1 -receptor and the membrane depolarization in the isolated rat aortic strips, which seems to be associated to calcium influx.

KEY WORDS : Isolated rat aortic smooth muscle · Total Ginseng saponin · Vasoconstriction.

Acknowledgment

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