Original Article

Biphasic effects of sodium danshensu on vessel function in isolated rat aorta

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Aim: To investigate the effects of sodium danshensu on vessel function in isolated rat aortic ring.

Methods: Thoracic aortae from normal rats were isolated and equilibrated in organ bath with Krebs-Henseleit buffer and ring tension was recorded. Effects of sodium danshensu on basal tonus of the vessel and its effects on vessel contraction and relaxation with or without endothelium were observed.

Results: In thoracic arteries under basal tonus, sodium danshensu (0.3–3 g/L) produced a dose-dependent transient contraction. In phenylephrine-precontracted thoracic arteries with or without endothelium, low concentration (0.1–0.3 g/L) of sodium danshensu produced a weak contraction, while high concentrations (1–3 g/L) produced a pronounced vasodilator after a transient vasocontraction. Pre-incubation with sodium danshensu could inhibit vessel contraction induced by phenylephrine and potassium chloride in a concentration-dependent way. Sodium danshensu inhibited phenylephrine- and CaCl2-induced vasoconstriction in Ca2+-free medium. Pre-incubation with tetraethylammonium, a non-selective K+ channel blocker, and apamin, a small-conductance calcium-activated K+ channel blocker partially antagonized the relaxation response induced by sodium danshensu. However, iberiotoxin (big-conductance calcium-sensitive K+ channel blocker), barium chloride (inward rectifier K+ channel blocker), and glibenclamide (ATP-sensitive K+ channel blocker) had no influence on the vasodilatation effect of sodium danshensu.

Conclusion: Sodium danshensu showed a biphasic effects on vessel tension. While low dosage of sodium danshensu produced small contraction possibly through transient enhancement of Ca2+ influx, high dosage produced significant vasodilation mainly through promoting the opening of non-selective K+ channels and small-conductance calcium-sensitive K+ channels in the vascular smooth muscle cells.

Keywords: isolated aorta rings; sodium danshensu; vessel contraction and relaxation

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Introduction

Sodium danshensu [sodium D-(+)-β-(3,4-dihydroxyphenyl) lactate, C9H9O5Na, molecular weight 220, Figure 1] is a sodium salt of danshensu from the widely used Chinese herb Danshen (Salvia miltiorrhiza Bunge). As a traditional Chinese medicine, Danshen is mainly used for the treatment of cardiovascular diseases such as angina pectoris, myocardial infarction and stroke[1]. Danshensu is a water-soluble phenolic acids component in Danshen. In vitro and in vivo studies revealed that danshensu possessed diverse pharmacological effects, including relaxation of coronary artery, anticoagulation, protection of myocardial ischemia-reperfusion injury, and antiarrhythmia activities[2-4]. However, the effects of sodium danshensu on vessel function in isolated rat aorta are not well demonstrated. The present study was aimed to elucidate the effects of sodium dansh-
ensu on contraction and relaxation at various concentrations in rat thoracic aorta and the underlying mechanisms involved.

**Materials and methods**

**Procedure for isolation of sodium danshensu**

The root and rhizome of Salvia miltiorrhiza Bunge were collected in Hebei Province of China, and identified by Prof Han-cheng ZHENG from the Department of Pharmacognosy, School of pharmacy, Second Military Medical University, Shanghai, China. A voucher specimen has been deposited in the herbarium of the School of pharmacy, Second Military Medical University, Shanghai, China. Danshensu was isolated from the root and rhizome of Salvia miltiorrhiza Bunge. Briefly, the dried and powdered roots and rhizomes (1.0 kg) were extracted under thermal reflux for 2 h with H2O (12 L) accommodated with H2O (12 L) and powdered roots and rhizomes (1.0 kg) were extracted under thermal reflux for 2 h with H2O (12 L) and then maintained at 37 °C. One stirrup was connected to an isometric force transducer for tension measurement and recording with a data-acquisition system (MPA 2000; Alcott Biotech, Shanghai, China).

The rings were stretched to a resting tension of 2.0 g and allowed to achieve equilibrium for 60 min with the bath fluid being changed every 15 min. In some rings, the endothelium was removed mechanically by inserting a polyethylene tube into the lumen of the ring and rolling the vessel with the tube gently onto moistened gauze. Endothelial integrity was assessed by degree of relaxation caused by acetylcholine (1 µmol/L) in the presence of contractile tone induced by phenylephrine (PE) (1 µmol/L). For the studies of endothelium-intact vessels, the ring was discarded if relaxation with acetylcholine was less than 80%. For studies of endothelium-denuded vessels, the rings were discarded if there was any degree of relaxation.

**Effect of sodium danshensu on the basal tone of aortic ring**

After equilibration, endothelium-denuded rings were incubated with various concentrations of sodium danshensu (0.3, 1, or 3 g/L) respectively for 30 min, and the time-response curves for sodium danshensu was determined.

**Effects of Ca2+-free solution on the vasoconstriction of sodium danshensu**

In order to investigate whether Ca2+ influx was related to the vasoconstriction of sodium danshensu, the normal Krebs-Henseleit solution was replaced for a Ca2+-free solution containing EGTA (1 mmol/L), and endothelium-denuded rings were incubated with sodium danshensu (0.3, 1, or 3 g/L) for 30 min to obtain the time-response curves at various concentrations of sodium danshensu.

**Effect of sodium danshensu on thoracic aorta rings pre-contracted with phenylephrine**

After achieving equilibrium, phenylephrine (1 µmol/L) evoked a steady contraction in endothelium-intact and endothelium-denuded rings, and then, sodium danshensu (0.3, 1 or 3 g/L) was added respectively. The tension of each aorta ring was observed and recorded for 30 min after drug administration.

**Effect of sodium danshensu on contractions induced by phenylephrine and KCl**

After a 30-min incubation period with various concentrations of sodium danshensu (0.3, 1, or 3 g/L), cumulative concentration-response curves for phenylephrine (ranging from 1 mmol/L to 100 µmol/L) and KCl (ranging from 10 mmol/L to 90 mmol/L) were determined in endothelium-denuded rings.

**Effect of sodium danshensu on contraction induced by CaCl2**

To assess the effects of sodium danshensu on CaCl2-induced contractions, in this group of experiment, only one response is obtained with each vessel ring. Endothelium-denuded rings were first contracted with phenylephrine (1 µmol/L) to deplete the intracellular Ca2+ stores in Ca2+-free solution containing 1 mmol/L ethyleneglycoltetraacetic acid (EGTA) for approximately 60 min. The rings were then rinsed in Ca2+-free solution without EGTA containing 30 mmol/L KCl. At this time, if CaCl2 was added, CaCl2-induced vasoconstriction is through Ca2+ influx from the extracellular medium. The contractions induced by CaCl2 (0–2.5 mmol/L) were obtained in the absence of sodium danshensu (control group) or after a 30-min period incubation with sodium danshensu (0.3, 1, or 3 g/L).
Effect of sodium danshensu on Ca$^{2+}$ release from intracellular stores sensitive to phenylephrine

In order to investigate whether sodium danshensu could interfere with Ca$^{2+}$ release from intracellular stores, the normal Krebs-Henseleit solution was replaced by a Ca$^{2+}$-free solution containing EGTA (1 mmol/L). The endothelium-denuded rings were exposed to Ca$^{2+}$-free solution for 15 min and then stimulated with phenylephrine 1 µmol/L. The contractions were obtained in the absence (control group) or after a 30-min incubation period with sodium danshensu (0.3, 1, or 3 g/L).

Influence of K$^{+}$ channel blockers on sodium danshensu-induced vasorelaxation

To further investigate the possible mechanisms responsible for sodium danshensu-induced relaxation, which was found to be non-endothelium dependent, endothelium-denuded rings were pre-incubated with one of the following K$^{+}$ channel blockers: tetraethylammonium (TEA, 10 mmol/L), iberiotoxin (0.1 µmol/L), glibenclamide (3 µmol/L), apamin (0.1 µmol/L), barium chloride (BaCl$_2$, 30 µmol/L), or a mixture of TEA (10 mmol/L) and apamin (0.1 µmol/L) for 10 min before phenylephrine was added, and when the contractile plateau was attained, sodium danshensu (3 g/L) was added. Since glibenclamide was prepared in dimethylsulfoxide (DMSO), a DMSO control group was used with the same volume in glibenclamide group.

Measurement of cGMP content in thoracic aorta

The vessel rings with endothelium were stretched to a resting tension of 2.0 g and allowed to be equilibrated for 30 min with the bath fluid being changed every 15 min. Sodium danshensu (0.3, 1, and 3 g/L) was added to the bath and incubated for 30 min. Then the tissues were weighed and homogenized in cold acetic acid (50 mmol/L, pH 4.75). The homogenates were centrifuged at 13 000 g for 10 min and extracted twice with alcohol for 5 min. After centrifugation, the supernatant was collected in a glass bottle and dried for determination of cGMP using a radioimmunoassay kit (Shanghai Traditional Medicine University Medical Radiology Lab, Shanghai, China) according to the manufacturer’s protocol.

Reagents

Phenylephrine hydrochloride, acetylcholine hydrochloride, tetraethylammonium, iberiotoxin, apamin, glibenclamide, ruthenium red, ethyleneglycoltetraacetic acid (EGTA) and DMSO were all purchased from Sigma-Aldrich (St Louis, MO, USA). Verapamil hydrochloride injection was purchased from Shanghai Harvest pharmaceutical Co, Ltd. And phentolamine mesilate injection was purchased from Shanghai Sunrise Pharmaceutical Co, Ltd. Sodium danshensu was dissolved with Krebs-Henseleit solution. Glibenclamide was prepared as stock solution in DMSO. The other drugs were dissolved in distilled water. The bath concentration of distilled water or DMSO did not exceed 0.2%, which was shown to have no effect per se on the basal tonus of the preparations or on the agonist-mediated contraction or relaxation.

Statistical analysis

All results are expressed as mean±SEM. Statistical analysis was performed by unpaired Student’s t-test for observations between two groups or by ANOVA for comparisons of multiple groups. A value of $P<0.05$ was considered statistically significant.

Results

Effect of sodium danshensu on the basal tonus

In normal Krebs-Henseleit solution, for aorta rings in basal tonus states, sodium danshensu first caused a contraction which achieved the maximum at about the eighth minute, and then followed by a spontaneous relaxation. The maximal contraction is 0.86±0.04 g, 1.46±0.03 g and 1.49±0.05 g for sodium danshensu 0.3 g/L, 1 g/L, and 3 g/L respectively (data are mean±SD, n=12–15 segments for each group, Figure 2A).

In Ca$^{2+}$-free solution, the transient contraction induced by sodium danshensu was markedly reduced compared with that in normal Krebs-Henseleit solution, although not being deleted completely (Figure 2B).

Biphasic effect of sodium danshensu on PE-precontracted aorta

It can be seen in Figure 3A, in phenylephrine pre-contracted rat thoracic aorta, as compared with control (Figure 3Aa),
sodium danshensu caused small contraction at the concentrations ranging from 0.1 g/L to 0.3 g/L (Figure 3Ab and Figure 3Ac), but at the concentrations ranging from 1 g/L to 3 g/L (Figure 3Ad, Figure 3Ae, and Figure 3Af), sodium danshensu produced a biphasic response: a transient contraction followed by a pronounced relaxation. There was no difference in the contraction or vasodilation responses to sodium danshensu between vessel with and without endothelium (Figure 3B).

**Effects of sodium danshensu incubation on PE- and KCl-induced contraction**

The effects of sodium danshensu on the cumulative concentration-response curves for phenylephrine and KCl on isolated rat thoracic aorta are shown in Figure 4 and Figure 5. The tension for phenylephrine or KCl in endothelium-denuded rings were depressed in the presence of sodium danshensu.

**Effect of sodium danshensu on CaCl₂-induced contraction**

Pretreatment with sodium danshensu attenuated CaCl₂-induced contraction of denuded rat aorta exposed to Ca²⁺-free solution containing KCl. Preincubation of the rings with sodium danshensu at the contraction of 3 g/L significantly reduced the contraction induced by CaCl₂ (Figure 6).

**Effect of sodium danshensu on intracellular Ca²⁺ release**

The results presented in Figure 7 show that sodium danshensu significantly inhibited the contractions induced by phenylephrine in Ca²⁺-free solution containing EGTA. In Ca²⁺-free solution, the maximum contraction elicited by phenylephrine was 0.18±0.03 g in control group, and this was attenuated to 0.16±0.02 g, 0.12±0.03 g, and 0.09±0.01 g (50% reduction; n=5

![Figure 3](image_url)

**Figure 3.** Representative tracing of vessel contraction and relaxation at different concentrations (A) and dose- and time-dependent vasoactive effects of sodium danshensu in aortic rings with and without endothelium (B).

![Figure 4](image_url)

**Figure 4.** Effects of sodium danshensu on phenylephrine-induced contractile response in endothelium-denuded rat aortic rings. The responses were determined after 30-min pre-incubation with sodium danshensu. Data are mean±SD. n=6–7 segments.

![Figure 5](image_url)

**Figure 5.** Effects of sodium danshensu on KCl-induced contractile response in endothelium-denuded rat aortic rings. The responses were determined after 30-min pre-incubation with sodium danshensu. Data are mean±SD. n=6–7 segments.
Influence of potassium channel blockers on sodium danshensu-induced vasorelaxation

In order to examine the role of specific types of K⁺ channels in the sodium danshensu-induced response, aortic rings were incubated with either TEA (10 mmol/L), iberiotoxin (0.1 µmol/L), glibenclamide (3 µmol/L), barium chloride (30 µmol/L), or a mixture of TEA (10 mmol/L) and apamin (0.1 µmol/L) for 10 min prior to the application of phenylephrine. Sodium danshensu (3 g/L) was added after the contraction to phenylephrine reached plateau and vessel tension was observed for 30 min. In the presence of TEA (a non-selective K⁺ channel blocker), vasorelaxation effect of sodium danshensu was partially inhibited. Similarly, apamin (a small-conductance KCa channel blocker) also caused a significant inhibition of relaxation partially. The combination of non-selective K⁺ channel blocker TEA (10 mmol/L) and apamin (0.1 µmol/L) also produced partial inhibition of relaxation significantly. However, iberiotoxin (a big-conductance calcium-sensitive K⁺ channel blocker), barium chloride (a inward rectifier K⁺ channel blocker) and glibenclamide (a ATP-sensitive K⁺ channel blocker) did not affect the relaxation effect of sodium danshensu (Figure 8).

Effect of sodium danshensu on the concentration of cGMP in rat thoracic aorta

The content of cGMP in rat thoracic aorta with endothelium was significantly depressed after being incubated with sodium danshensu (Figure 9). This result indicated the role of the cGMP pathway in the vasoconstriction effect of sodium danshensu.

Discussion

The present study revealed a biphasic response to sodium danshensu in both basal-equilibrated and contracted thoracic arteries. In basal tonus aortic rings, sodium danshensu produced a transient contraction followed by a spontaneous vasodilator response in endothelium-denuded aortic rings. In phenylephrine pre-contracted thoracic arteries, low concentration of sodium danshensu produced a small contraction, and sodium danshensu in high concentrations produced transient small contractions followed by significant vasodila-
Vasoconstriction responses. In Ca²⁺-free solution, the contraction may play an important role in sodium danshensu-mediated vasoconstriction. Our results revealed that sodium danshensu had a similar effect to danshen capsule, as it produced marked vasodilatation. Our results indicated that sodium danshensu may be the main component that induced the biphasic response among the components from danshen.

Figure 9. Effect of sodium danshensu on the content of cGMP in rat thoracic aorta with endothelium. The content of cGMP in rat thoracic aorta with endothelium was significantly depressed after being incubated with sodium danshensu, in a dose-dependent manner. *P<0.05, **P<0.01 vs control.

Mechanisms in sodium danshensu-induced vessel dilation

Sodium danshensu in high concentrations constantly produced a significant vasodilation response after transient contraction, whether the endothelium is removed or not, indicating smooth muscle-dependent vasodilation.

Different mechanisms may be involved in sodium danshensu-induced vessel relaxation. Sodium danshensu may exert vasodilation through inhibiting extracellular calcium influx and phenylephrine-sensitive endogenous calcium release, as we found that preincubation of sodium danshensu could inhibit calcium-induced vasoconstriction in endogenous calcium-depleted state as well as phenylephrine-induced contraction in calcium-free buffer. This is in consistent with the report that danshensu produced vasodilator action in isolated rat coronary arteries at a concentration range of 0.02 to 0.035 mg/mL, mainly by inhibition of Ca²⁺ influx[5]. Phenylephrine and potassium chloride induced contraction are both through increasing intracellular Ca²⁺ concentration but with different cellular mechanisms. Phenylephrine activates the receptor-operated Ca²⁺ channel and induces an influx of extracellular Ca²⁺. Simultaneously, phenylephrine mobilizes Ca²⁺ release from intracellular stores through binding to α₁-adrenoceptor and stimulating phospholipase C or the specific IP₃ receptor (IP₃R) channel in sarcoplasmic reticulum (SR) membrane[8]. Potassium chloride induces Ca²⁺ influx through voltage-dependent Ca²⁺ channel, which further activate Ca²⁺-induced Ca²⁺ release through a ryanodine receptor[9].

In Ca²⁺-free medium containing EGTA, phenylephrine-
induced vasoconstriction is through activating the IP$_3$R channel in sarcoplasmic reticulum membrane and inducing the release of intracellular Ca$^{2+}$ release from sarcoplasmic reticulum.\[6, 11\] In our study, sodium danshensu dose-dependently reduced phenylephrine-induced contraction in Ca$^{2+}$-free medium, demonstrating that sodium danshensu can reduce Ca$^{2+}$ release from intracellular stores sensitive to phenylephrine.\[12\] After aortic rings first were contracted with phenylephrine to deplete the intracellular Ca$^{2+}$ stores in Ca$^{2+}$-free medium containing EGTA and then rinsed in Ca$^{2+}$-free medium (without EGTA) containing KCl, CaCl$_2$-induced vasoconstriction is through Ca$^{2+}$ influx from the extracellular medium.\[12\] In the present study, CaCl$_2$-induced vasoconstriction in Ca$^{2+}$-free medium containing KCl was inhibited significantly by sodium danshensu, indicating that sodium danshensu behaved as a non-selective calcium antagonist. This is in agreement with a recent study with rat coronary artery.\[3\] Taken together, these results demonstrated that sodium danshensu could block Ca$^{2+}$ influx and reduce Ca$^{2+}$ release from intracellular stores sensitive to phenylephrine.

Direct activation of K$^+$ channels on arterial smooth muscle cells normally hyperpolarizes the cell membrane, inhibits Ca$^{2+}$ influx through voltage-operative Ca$^{2+}$ channel, and suppresses smooth muscle contraction.\[13-15\] To further explore whether a particular K$^+$ channels is involved in the sodium danshensu-induced vasorelaxation in high concentrations, various of potassium channel blockers was used as tools in the present study. TEA, a non-selective K$^+$ channel blocker, significantly inhibited the vasorelaxation partially. Apamin, a small-conductance K$_{Ca}$ channel blocker, also caused partial inhibition of the sodium danshensu-induced relaxation. However, big-conductance calcium-sensitive K$^+$ channel inhibitor iberiotoxin did not alter the relaxation effect of sodium danshensu, which is in accordance with a previous finding on porcine coronary artery smooth muscle cells.\[16\] Similarly, the blockade of inward rectifier K$^+$ channel and ATP-sensitive K$^+$ channel did not affect the relaxation response of sodium danshensu. These findings indicated that activation of non-selective K$^+$ channel and small-conductance calcium-sensitive K$^+$ channel in the vascular smooth muscle cells may also contribute to vasorelaxation to some extent. Because either non-selective K$^+$ channel blocker TEA or small-conductance K$_{Ca}$ channel blocker apamin produced only partial inhibition, did not abolish the vasodilator of sodium danshensu, the mixture of the two kinds of K$^+$ channel inhibitors were tested. The mixture of the two kinds of K$^+$ channel inhibitors also could not abolish the vasodilator of sodium danshensu entirely though could produce significant inhibition partially. This further consolidates the view that except direct opening of K$^+$ channels, there are other pathways for sodium danshensu producing the vessel dilation.

As the concentration of sodium danshensu induced vasodilation is very high, nonspecific action could not excepted. In conclusion, the present study has indicated that sodium danshensu showed a biphasic effect in isolated rat thoracic aorta rings. While low contractions of sodium danshensu produced small vasoconstrictor responses by enhancing transient extracellular Ca$^{2+}$ influx and reducing the vessel content of cGMP, high concentrations of sodium danshensu produced pronounced vasodilator responses through blocking calcium influx and inhibiting intracellular calcium release, as well as opening non-selective K$^+$ channel and small conductance calcium-sensitive K$^+$ channels in the vascular smooth muscle cells. The calcium influx promotion and inhibition induced by sodium danshensu during contraction and relaxation may involve different channels and needs further exploration, and using an electrophysiological method to record the Ca$^{2+}$ current may assist to interpret this phenomenon.

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Author contribution
Ning ZHANG, Chuan ZHANG and Hong CHEN designed the research; Ning ZHANG, Mei-fang ZHONG, Hao ZOU, Jian WANG and Lei JIN performed the research; Chuan ZHANG and Hong CHEN contributed new reagents and analytical tools; Peng HUANG and Bing-qing GU carried out the preliminary experiment; Ning ZHANG analyzed data; Ning ZHANG wrote the paper; Chuan ZHANG, Hong CHEN, and Shi-long MAO revised the paper.

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