

Cardiovascular Pharmacology of Sinomenine: The Mechanical and Electropharmacological Actions

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Abstract: Sinomenine is one of the alkaloids extracted from Chinese medical plant, *Sinomenium acutum* Rehder et Wilson. Sinomenine has been used for Rheumatoid arthritis as an anti-inflammatory and immunomodulative drugs. We have so far been investigated the cardiovascular pharmacological actions of sinomenine. Sinomenine dilated NE (5 μ M)-, KCl (60 mM)- and PDB (300 nM)-induced vasoconstrictions. The pretreatment with nicardipine (0.1 μ M), staurosporine (30 nM), L-NMMA (100 μ M), indomethacin (10 μ M) or propranolol significantly attenuated the sinomenine-induced vasorelaxation. Therefore, these results indicate that sinomenine causes the vasorelaxation by the involvement with the inhibitions of Ca^{2+} current (I_{Ca}) and PK-C, β -adrenoceptor stimulation, and the activation of NO and PGI₂ syntheses in endothelium. On the other hand, in the ventricular cardiomyocytes of guinea pig, sinomenine inhibits I_{Ca} and simultaneously decreases the delayed rectifier K^+ current (I_K), resulting in the prolongation of action potential duration. Sinomenine also suppresses the dysrhythmias induced by triggered activities under the Ca^{2+} overload condition. Therefore, sinomenine may be expected as one of effective therapeutic drugs for heart failure and dysrhythmias, and may maintain the cardiovascular functions due to modulation of cardiac ionic channels and blood vessels.

Keywords: Sinomenine, Vasodilation, Cardioprotective action, Ca^{2+} channel, Aorta, Cardiomyocytes

Introduction

Sinomenine (7, 8-didehydro-4-hydroxy-3, 7-dimethoxy-17-methyl-9 α ,13 α ,14 α -morphinan-6-one) is one of the alkaloids extracted from Chinese herbs, *Sinomenium acutum* Rehder et Wilson (Li et al. 2004) or *Sinomenium acutum* var. cinereum (Zhao et al. 2005). In Chinese traditional medicine, *Sinomenine acutum*, a vine plant, has been used for rheumatic diseases for thousands years (Yamasaki, 1976; Liu et al. 1996). Its main constituent of *Sinomenine acutum* is sinomenine, which has also used for clinical treatment of Rheumatoid arthritis (RA), due to the anti-inflammatory and immunomodulative actions (Yamasaki, 1976; Liu et al. 1996).

We have already investigated the cardiovascular pharmacological actions of sinomenine. Mokuboito (Mu-Fang-Yi-Tang), a kind of Kampo formulation containing *sinomenium acutum*, has been used for heart failure (Inaki et al. 2005), which improves heart failure symptom and reduces New York Heart Association (NYHA) class and plasma brain natriuretic peptide (BNP) concentration (Yakubo et al. 2002). Mokuboito consists of Sinomeni Caulis et Rhizoma (rhizome of *Sinomenium acutum* Rehder et Wilson), Cinnamomi Cortex (bark of *Cinnamomum cassia* Blume), Ginseng Radix (roots of *Panax ginseng* C. A. Meyer) and Gypsum Fibrosum. In our recent reports (Satoh, 2005; Nishida and Satoh, 2006; 2007), Mokuboito, *Sinomenium acutum* and sinomenine might improve chronic heart failure, resulting from the modulation of cardiac and vascular systems. Mokuboito can exert the vasodilating and cardioprotective actions (Satoh, 2005), as discussed in the following parts.

In general, the basic treatments of heart failure consist of (1) reducing workload of heart, (2) protection of cardiomyocytes and (3) restriction and control of waters and sodium. In order to reduce both pre- and after-loads, the dilations of arterioles and veins are strongly required in the case of elevated filling pressures and reduced cardiac output. As a cardiovascular protective drug, sinomenine might contribute to clinical treatments via modulation of the ionic currents of cardiac cells, and control of the tension of blood vessels.

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In this review, the cardiovascular pharmacological actions of sinomenine are mainly shown and discussed.

Source of Sinomenine

Sinomenine is derived from natural plant such as *Sinomenium acutum* (Li et al. 2004) and *Sinomenium acutum* var. *cinereum* (Zhao et al. 2005). *Sinomenium acutum* and *Sinomenium acutum* var. *cinereum* are widely in a lot of regions of China. *Caulis sinomeni* is the dried plant stems of *Sinomenium acutum* and *Sinomenium acutum* var. *cinereum*. There is less or no difference in sinomenine content of *Caulis sinomeni* between the species and the varieties of growing regions. The variation is found among the samples collected from different parts of plant. The content of sinomenine is dependent on the size (diameter) of stem. The sinomenine content in *Sinomenine acutum* is 1.63 ± 0.64 (% w/w) in large (>3 cm) stem, 0.96 ± 0.45 (% w/w) in 1–3 cm stem, and 0.49 ± 0.16 (% w/w) in <1 cm stem (Zhao et al. 2005).

Pharmacokinetics of Sinomenine

The pharmacokinetics and tissue distribution of sinomenine have been studied in rats (Liu et al. 2005). Sinomenine achieves high bioavailability (about 80%) by oral administration of 90 mg/kg. At 45 min later, sinomenine is found widely in internal organs such as kidney, liver, lung, spleen, heart, brain and testis. Sinomenine is metabolized and eliminated by kidney and liver. T_{max} is 39.5 ± 8.49 min, C_{max} is 13.89 ± 4.29 μ g/ml, $T_{1/2A}$ phase is 61.28 ± 53.62 min, AUC_{0-t} is 2331.53 ± 1172.77 μ g-min/ml, and C_L is 42.95 ± 14.4 ml/min per Kg.

In clinical studies, oral administration of 80 mg sinomenine is performed for healthy volunteers (Yan et al. 1997). In the pharmacokinetic parameters, $T_{1/2\alpha}$ is 1.04 ± 0.491 h, $T_{1/2\beta}$ is 9.397 ± 2.425 h, T_{max} is 1.04 ± 0.274 h, C_{max} is 246.6 ± 71.165 ng/ml. Furthermore, AUC is 2651.158 ± 1039.050 ng.h/ml, and C_L is 0.033 ± 0.010 ng/ml.

Vascular Pharmacology

Male Wistar rats (5–10 week-old) were anesthetized with ether, and euthanized by exsanguination. The thoracic aorta was quickly removed, and then the isolated aorta was cut into rings of 3-mm in length. All rings were stretched to generate a resting tension of 1.2 g in Krebs solution. After 40

min of resting, norepinephrine (NE) (5 μ M) was added to the tissue bath. After the contractile response became steady, the drugs were cumulatively administrated into the bath solution. The similar methods are described in our previous reports (Nishida and Satoh, 2003; 2006).

The aorta ring strip of rat had a strong contraction after an initial application of 5 μ M NE. Sinomenine (0.1 to 100 μ M) applications potently relaxed the contraction induced by NE in a concentration-dependent manner (Nishida and Satoh, 2006). The relaxation was produced at the concentrations of over 0.3 μ M sinomenine, and at 100 μ M decreased the contractions by $68.8 \pm 5.1\%$ ($n = 6$, $p < 0.001$). PDB (300 nM) and KCl (60 mM) also caused strong contractions. Sinomenine dilated both PDB- and KCl-induced contractions in a concentration-dependent manner; at 100 μ M by $49.9 \pm 9.8\%$ ($n = 6$, $p < 0.001$) and $86.9 \pm 8.5\%$ ($n = 6$, $p < 0.001$), respectively (Fig. 1). Furthermore, the relaxation of sinomenine (0.1 to 100 μ M) was attenuated significantly by the pretreatment with nicardipine (Fig. 2). At 100 μ M the relaxation decreased from $68.8 \pm 5.1\%$ ($n = 6$) to $35.5 \pm 6.9\%$ ($n = 5$, $p < 0.001$). Since PK-C inhibition may be related to sinomenine-induced vasorelaxation, the pretreatment with staurosporine (30 nM) for 30 min was carried out (Satoh, 1996; Nishida and Satoh, 2004). Staurosporine attenuated the sinomenine-induced vasorelaxation; at 100 μ M from $68.8 \pm 5.1\%$ ($n = 6$) to $49.5 \pm 7.7\%$ ($n = 5$, $p < 0.001$) (Fig. 2). In addition, propranolol (0.3 μ M) also significantly attenuated the sinomenine-induced relaxation. The vasorelaxation at 100 μ M sinomenine was attenuated to $45.2 \pm 4.2\%$ ($n = 5$, $p < 0.01$).

Therefore, the modulation of both Ca^{2+} channel and PK-C is largely contributed to sinomenine-induced actions, and sinomenine also vasodilates mediated through β -adrenoceptor stimulation of aortic smooth muscle cells.

For involvement with endothelium-dependent relaxation via NO activation, a pretreatment with 100 μ M L-NMMA (a non-selective NO synthesis inhibitor) was carried out (Nishida and Satoh, 2003; 2007). Under the conditions, the vasorelaxation induced by sinomenine was attenuated from $68.8 \pm 5.1\%$ ($n = 6$) to $25.3 \pm 2.3\%$ ($n = 5$, $p < 0.01$) (Fig. 2). The attenuation was supported by the results using the aorta with removal of endothelium; at 100 μ M sinomenine by $53.7 \pm 1.8\%$ ($n = 5$, $p < 0.01$). Indomethacin (10 μ M), as an

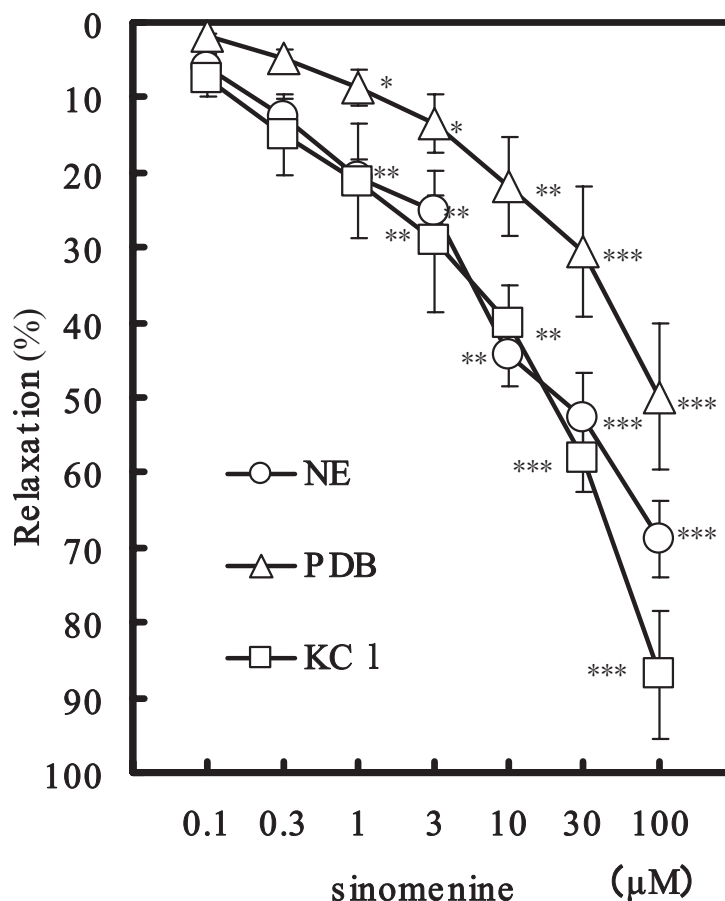


Figure 1. Concentration-dependent relaxation of sinomenine on NE-, PDB- and KCl-induced vasorelaxations. Symbols used are sinomenine in pretreatments with NE (open circles, $n = 6$), PDB (triangles, $n = 6$) and KCl (squares, $n = 6$). Values (%) represent mean \pm S.E.M. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, with respect to control value.

inhibitor of prostanoid production, also strongly reduced the vasorelaxation induced by 100 μM sinomenine to $37.1 \pm 9.3\%$ ($n = 5$, $p < 0.001$). Thus, both L-NMMA and indomethacin affected the sinomenine-induced relaxation significantly. Therefore, sinomenine possesses the pharmacological characteristics for modulation of NO synthesis and PG production, as well as the inhibitions of Ca^{2+} channel and PK-C and the stimulation of β -adrenoceptor. The possible mechanisms for the vasodilating actions of sinomenine are summarized in Fig. 3.

Cardiac Electropharmacology

Cardiac cells were taken from the ventricle muscles of guinea pig hearts, using methods similar to those described previously (Sato, 2003, 2005). Current-clamp and whole-cell voltage-clamp were performed using an Axopatch patch-clamp amplifier (Axon Instruments, Burlingame, C.A, U.S.A.) and standard techniques.

Current-clamp experiments were carried out to examine the modulation of the action potential configuration in guinea pig ventricular muscles (Fig. 4A) (Sato, 2005). Sinomenine at 300 μM and 1 mM increased the 75% repolarization of action potential duration (APD_{75}) by $24.9 \pm 3.5\%$ ($n = 6$, $p < 0.05$) and by $43.7 \pm 3.3\%$ ($n = 6$, $p < 0.001$), respectively. Sinomenine at 1 mM decreased the amplitude (APA), but not significantly ($0.9 \pm 2.1\%$, $n = 5$). The resting potential was not affected.

The modulation of L-type Ca^{2+} current (I_{Ca}) was investigated. Test pulses were applied to 0 mV from a holding potential of -30 mV. The average capacitance was 84.1 ± 2.4 pF ($n = 23$). At 1 mM sinomenine inhibited the I_{Ca} at 0 mV by $18.2 \pm 2.1\%$ ($n = 6$, $p < 0.05$). At 1 mM, the delayed rectifier K^{+} currents (I_{K}) at 60 mV was inhibited by $16.2 \pm 2.6\%$ ($n = 6$, $p < 0.05$) (Fig. 4B), and the inwardly rectifying K^{+} current (I_{K1}) at -120 mV by $47.2 \pm 3.8\%$ ($n = 6$, $p < 0.01$).

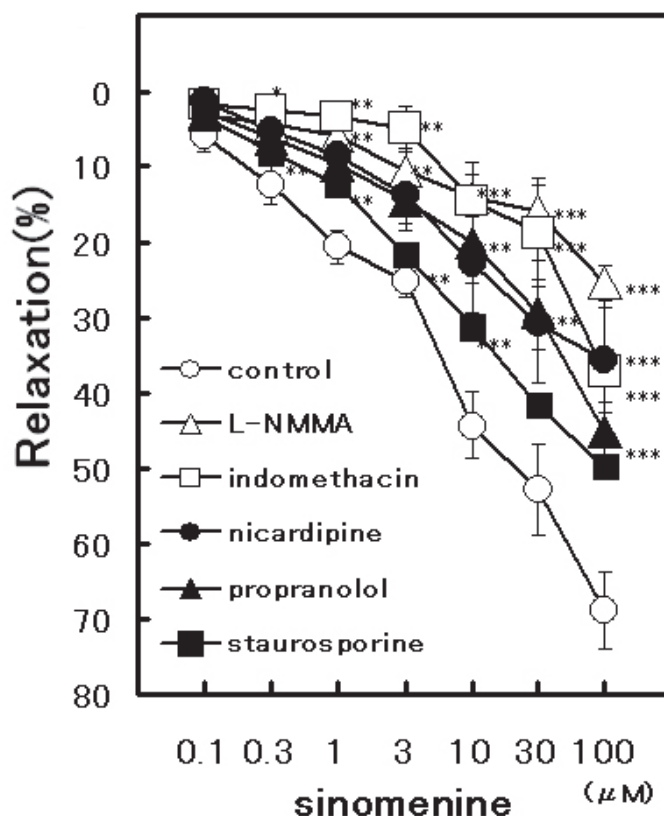


Figure 2. Modulation by several inhibitors of the relaxation induced by sinomenine. Symbols used are in the absence (open circles, $n = 6$), in the presence of $100 \mu\text{M}$ L-NMMA (open triangles, $n = 5$), $10 \mu\text{M}$ indomethacin (open squares, $n = 5$), $0.1 \mu\text{M}$ nicardipine (closed circles, $n = 5$), $0.3 \mu\text{M}$ propranolol (closed triangles, $n = 5$), and 30 nM staurosporine (closed squares, $n = 5$). Values (%) represent mean \pm S.E.M. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, with respect to control value.

In multicellular preparations, the modulation of action potential configuration by sinomenine was also examined (Satoh, 2005). The preparations were stimulated at 1 Hz. Sinomenine ($100 \mu\text{M}$ to 1 mM) had inhibitory effects on the action potentials, and tended to increase the action potential durations (APD); at 1 mM , by $4.1 \pm 1.6\%$ ($n = 6$) in APD_{50} and by $4.5 \pm 1.4\%$ ($n = 6$) in APD_{90} (but not significantly). The maximum rate of depolarization (V_{max}) was also inhibited by $20.0 \pm 2.4\%$ ($n = 6$, $p < 0.05$) at $300 \mu\text{M}$ and by $32.1 \pm 3.3\%$ ($n = 6$, $p < 0.05$) at 1 mM of sinomenine.

In high extracellular Ca^{2+} ($[\text{Ca}^{2+}]_o$) solution (5.4 mM) to cause cellular Ca^{2+} overload, abnormal action potentials occurred irregularly, in spite of constant stimulation (1 Hz) (Satoh, 2005). Application of $300 \mu\text{M}$ sinomenine suppressed and abolished the abnormal action potentials (dysrhythmias) (Fig. 5).

The changes in the action potential configurations and the modulation of the ionic channel

currents on the membrane of cardiomyocyte by sinomenine are summarized in Fig. 6.

Immunomodulative Action

Sinomenium acutum has been used for treatment for various rheumatic diseases as a Chinese traditional medicine (Yamasaki, 1976; Liu et al. 1996). In basic pharmacological studies of *Sinomenium acutum*, the inhibitory actions on some enzymes relating to inflammation have been shown (Li et al. 2003).

One of most famous pharmacological actions of sinomenine is an immunomodulative effect. Sinomenine is also clinically used for RA treatment (Yamasaki, 1976; Liu et al. 1996). A lot of reports concerning about not only an anti-rheumatic effect, but also anti-inflammatory and immunomodulative effects have already been shown. As anti-rheumatic direct effects, it has been reported that sinomenine reduces inflammatory parameters and attenuates proliferation of

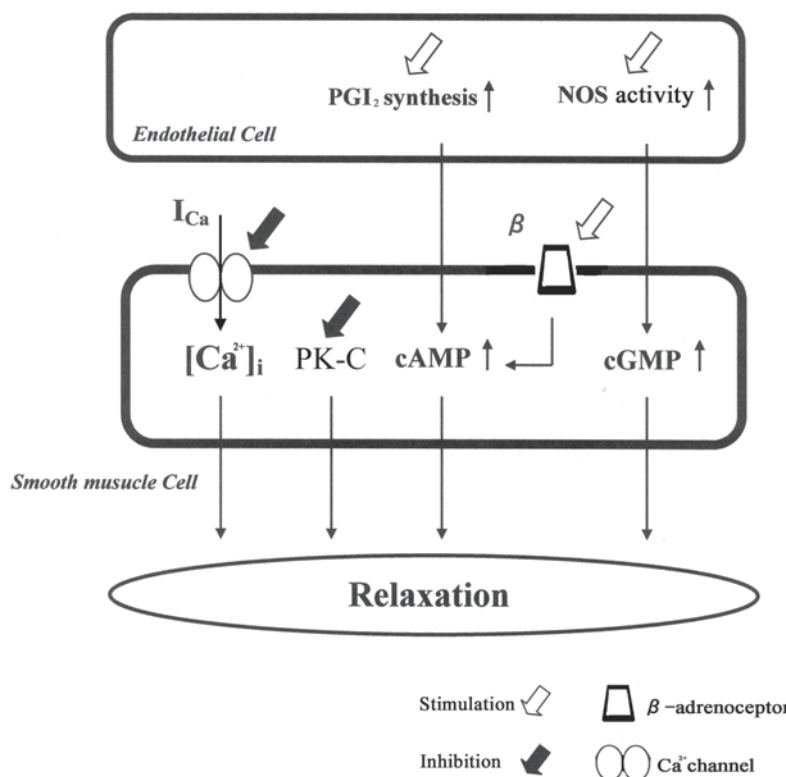


Figure 3. Summary of the multiple mechanisms induced by sinomenine. Sinomenine produces the vasorelaxation via NO and PGI₂ releases from endothelium. Also, sinomenine causes the vasorelaxation via modulation of Ca²⁺ channels and PK-C activity in smooth muscle cells. In addition, β -adrenoceptor stimulation is caused. NOS: nitric oxide synthetase, PK-C: protein kinase C, PGI₂: prostaglandin I₂.

synovial fibroblasts in rat adjuvant arthritis models (Liu et al. 1996). The anti-inflammatory and immunomodulative actions of sinomenine are responsible for various mechanisms via complex modulation of leukocytes and cytokine. Sinomenine reduces the production of prostaglandin (PG) E₂ and NO from macrophage (Liu et al. 1994a). Also, sinomenine possesses anti-proliferative effects on lymphocytes (Liu et al. 1994b), contributing to anti-inflammatory and anti-rheumatic effects. In addition, sinomenine depressed mRNA expression of tumor necrosis factor (TNF)- α and interleukin (IL)- β of peritoneal macrophages (Wang et al. 2005). Therefore, sinomenine may act as an anti-rheumatic drug through the anti-inflammatory effects on lymphocytes and cytokine. Sinomenine inhibited bFGF-induced angiogenesis in vitro and in vivo (Kok et al. 2005). Sinomenine also attenuates transmigration of granulocyte. The inhibition of leukocytes migration across the vessel wall and anti-angiogenic effect of sinomenine may also contribute to therapeutic effects for RA. Immunomodulative actions have been studied as the other aspect of sinomenine concerning about the

cardiac transplantation model. It has been reported that acute and chronic cardiac allograft ejections are blocked by the immunomodulatory effects of sinomenine (Mark et al. 2003).

Conclusion

Endothelium-dependent and -independent relaxations

We have been demonstrated that sinomenine possesses strong vasodilating actions by multiple mechanisms (Nishida and Satoh, 2006). The summarized mechanisms of sinomenine-induced vasorelaxation are shown in Fig. 3. Sinomenine possesses endothelium-dependent vasorelaxation via NO and PGI₂ releasing from endothelium. NOS activation and PGI₂ release are elicited by an increase in the intracellular Ca²⁺ concentration ([Ca²⁺]_i) in endothelium cells (Busse et al. 1998; Quignard et al. 1999). The mechanisms for the endothelium-dependent relaxations are not yet unclear. However, sinomenine might increase [Ca²⁺]_i in endothelium cells and then, activates

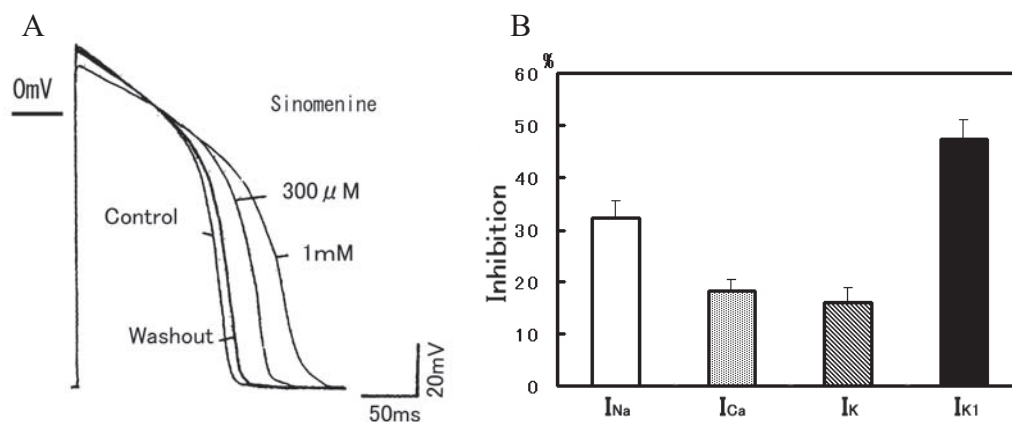


Figure 4. Modulation by sinomenine on the action potentials in guinea pig ventricular cardiomyocytes. **A:** Concentration-dependent changes in the action potential configuration by sinomenine. Short lines at the left of action potential recordings represent zero mV level. **B:** The percentage inhibitions by sinomenine of cardiac ionic currents. Vertical bars represent mean \pm SEM.

NOS activity and PGI₂ releasing, as reported previously (Nishida and Satoh, 2003).

Sinomenine causes the vasorelaxation via modulation of Ca²⁺ channels and PK-C activity in vascular smooth muscle cells. In vascular muscle cells, the contraction systems and the ion channels are regulated through the intracellular signal conditions (Satoh and Sperelakis, 1991, 1995; Satoh, 1996). Therefore, sinomenine might modulate the contraction systems, Ca²⁺ and Na⁺ channels, delayed rectifier K⁺ channels, and Ca²⁺-activated K⁺ (K_{Ca}) channel, accompanied with the activation of PK-C (Nishida and Satoh, 2007). Also, sinomenine

possesses β -adrenoceptor stimulating action to inhibit the aortic constriction.

Clinically possibility of cardiovascular pharmacological effects

Sinomenine is included in *Sinomenine acutum* of Mokuboito. Mokuboito is traditionally used for dyspnea and edema (Shuji et al. 2002). Therefore, sinomenine may be expected as one of the therapeutic agents for heart failure. Most recently, Satoh (2005) has demonstrated that sinomenine effectively modulates cardiac ionic channels. Sinomenine inhibits I_{Ca}, and simultaneously produces the I_K decrease in cardiomyocytes which results in the APD prolongation. Modulation of Ca²⁺ channel induced by sinomenine is similarly exerted in vascular smooth muscle cells. In addition, sinomenine possesses the regulatory actions for dysrhythmias under Ca²⁺ overload conditions. It has been well known that under the ischemia and heart failure, the cellular Ca²⁺ overload of heart muscles elicits some arrhythmias and dysfunctions (Satoh, 2001; 2003). The regulation of Ca²⁺ influx may modulate Ca²⁺ overload in cardiomyocytes and produces protective actions for Ca²⁺-overloaded myocardial cells (Satoh and Sperelakis, 1998). Therefore, sinomenine might restrain the cell damages of heart muscles via modulation of [Ca²⁺]_i, and as a result, exert a cardioprotective action.

Cardioprotective action of sinomenine on rat acute myocardial ischemia has also been demonstrated. Reperfusion injury is induced by ligating the rat left coronary artery for 15 min and reopening. Sinomenine can inhibit the incidence of

At 5.4 mM[Ca²⁺]_o.

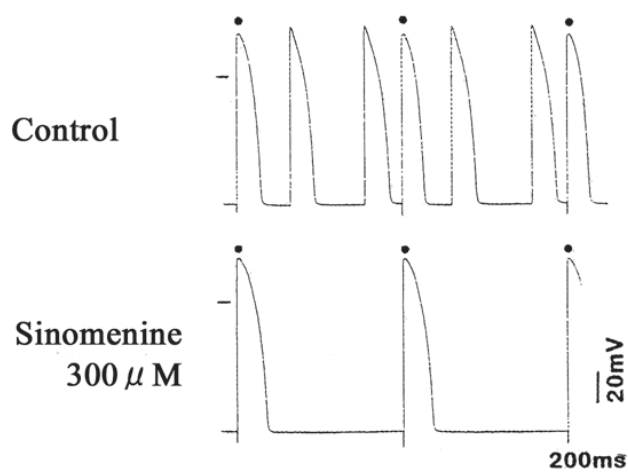


Figure 5. Antiarrhythmic actions of sinomenine in guinea pig papillary muscles. Sinomenine abolishes the abnormal action potentials in high Ca²⁺ concentration (5.4 mM). Dots above the action potential recordings are represented the regular rhythms induced by 1 Hz stimulation. The horizontal line indicates zero mV.

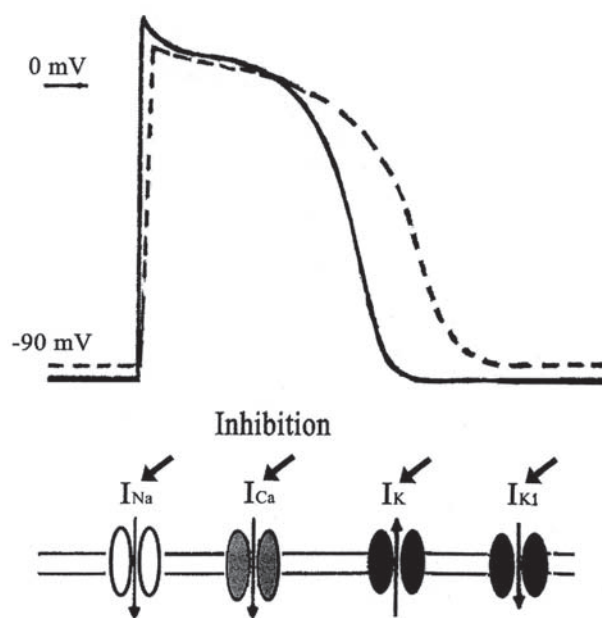


Figure 6. Same for the changes in cardiac ionic channels induced by sinomenine. Superimposed action potentials are in control (solid line) and in sinomenine (dash line). I_{Na} : the Na^+ channel, I_{Ca} : the Ca^{2+} channel, I_K : the delayed rectifier K^+ channel, I_{K1} : the inwardly rectifying K^+ channel.

arrhythmias and reduce intracellular Ca^{2+} concentration (Xie et al. 1993), well consistent with our results.

Sinomenine has multiple vasodilating mechanisms. The vasodilating agent is one of the great useful tools for heart failure and regulates pre- and after-loads of cardiovascular systems. Therefore, sinomenine-induced vasodilating actions may improve cardiac functions via the regulation of both pre- and after-loads under heart failure.

In summary, sinomenine caused a concentration-dependent vasorelaxation on NE-, KCl- and PDB-induced contractions, and sinomenine-induced vasorelaxation is attenuated by the pretreatments with L-NMMA, indomethacin, staurosporine, nicardipine and propranolol. In electropharmacological mechanisms, sinomenine inhibits the I_{Ca} and the I_K in cardiomyocytes which results in the APD prolongation. In addition, sinomenine depressed the dysrhythmias induced by triggered activities under the Ca^{2+} overload. Finally, sinomenine also possesses the anti-inflammatory and immunomodulative actions.

In future, therefore, sinomenine as a cardioprotective drug may be expected to the respectable effectiveness for heart failure, mediated through the modulation of cardiac ion channels (including the regulation for dysrhythmias) and blood vessels.

Further experiments need to elucidate more in detail mechanisms of sinomenine.

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