

Effects of tetrandrine on cardiovascular electrophysiologic properties

YAO Wei-Xing¹, JIANG Ming-Xing

Department of Pharmacology, Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430030, China

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ABSTRACT

Tetrandrine (Tet) is one of the best characterized Ca^{2+} channel blocker of plant origin. It can affect cardiovascular electrophysiologic properties in following field: inhibit the contractility, $\pm dt/dp_{\max}$, and automaticity of myocardium, prolong the FRP, and exert concentration-dependent negative inotropic and chronotropic effects without altering cardiac excitability.

Tet directly blocks both T-type and L-type calcium current in ventricular cells and vascular smooth muscle cells, but it does not shift the $I-V$ relationship curve of I_{Ca} . All its effects would be beneficial in the treatment of angina, arrhythmias, and other cardiovascular disorders.

Tet also directly inhibits the activity of BK_{Ca} channel in endothelial cell line and also inhibits Ca^{2+} -release-activated channels in vessel endothelial cells, which might significantly contribute to the change of endothelial cell activity.

INTRODUCTION

Tetrandrine (Tet) is a bis-benzylisoquinoline alkaloid isolated from the Chinese medicinal herb-root of *Stephania tetrandra* S Moore, which was traditionally used as an anti-inflammatory, antipyretic, and analgesic herb in Chinese medicine. Tet is active principle of the root of *Stephania tetrandra*. Empirical formula of Tet is $\text{C}_{38}\text{H}_{42}\text{O}_8\text{N}_2$ with molecular weight 622^[1]. The first pharmacological and toxicological study of Tet was published in 1937 which demonstrated its hypotensive and cardiodepressant effects^[2]. Since 1950s, Tet has been used in China as an antihypertensive agent^[3]. Subsequently, Tet has been shown to be a calcium an-

tagonist of plant origin^[4-7]. Recently, it was reported that Tet could protect hepatocytes against CCl_4 injury through anti-hepatic fibrosis effect^[8-9]; ameliorate development of pulmonary vascular and lung tissue injury induced by monocrotaline in rats^[10]; have potent immunosuppressive properties^[11]; be potentially useful in the treatment of silicosis^[12]; and treat hepatocellular carcinoma as chemotherapeutic/chemopreventive agent^[13].

During the past decade, Tet has received considerable attention mainly owing to its cardiovascular electrophysiologic properties as Ca^{2+} antagonist^[4,14-16]. It is believed that the inhibitory effect on Ca^{2+} influx is the basis of the cardiovascular action and therapeutic efficacy of Tet. Tet, in addition to its effects of blocking L- and T-type calcium channels, also produced an inhibition of BK_{Ca} ^[17] and the non-selective cation channels, *ie* characteristic of Ca^{2+} release-activated Ca^{2+}

¹ Correspondence to Prof YAO Wei-Xing.

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channel present in endothelial cells^[18]. This review focused on cardiovascular electrophysiologic effects of Tet.

EFFECTS ON MYOCARDIUM^[19-21]

Contractility, $\pm dt/dp_{\max}$, automaticity, FRP, and excitability Papillary muscle of cat right ventricle or guinea pig left atrium suspended in Tyrode's solution is stimulated by square wave. Isometric contractions and $\pm dt/dp_{\max}$ were recorded. After addition of Tet 32 $\mu\text{mol/L}$ for 5 min the force of contraction began to fall and decreased by 29 % (papillary muscle), 64 % (atrium) of the control level at the end of 15 min, and dt/dp_{\max} also declined coincidentally.

The threshold concentration of adrenaline to induce automaticity was compared before and after administration of Tet 32 $\mu\text{mol/L}$ at 37 °C. Tet increased the threshold concentration of adrenaline to induce automaticity in guinea pig by 15 fold.

Functional refractory period (FRP) was determined by paired impulses (3 ms, 0.2 Hz, 5 times threshold voltage), After administration of Tet 32 $\mu\text{mol/L}$, the FRP of guinea pig left atrium and cat papillary muscle were prolonged from (114 \pm 9) ms and (326 \pm 19) ms to (158 \pm 9) ms and (384 \pm 38) ms, respectively.

Excitability of myocardial preparation was determined with intensity-duration curves. There was no significant change in excitability after addition of Tet 32 $\mu\text{mol/L}$. It suggested that Tet had no effect on sodium channels on cell membrane.

Heart rate The effects of Tet 32 $\mu\text{mol/L}$ on guinea pig right atrium showed that it slowed down the rate of spontaneous beating of right atrium to 1/3 of its original level within 15 min, which indicated that Tet had an inhibitory effect on sinus node automaticity.

In isolated rabbit right atrium and cat papillary muscles, Tet could antagonize the positive chronotropic action of both CaCl_2 and isoprenaline in a non-competitive manner^[22]. Another study indicated that Tet also inhibited positive staircase phenomena and post-rest potentiation of contraction^[23].

In the intact rat ECG (II lead), repeated intravenous or continuous infusion of Tet decreased heart rate^[24]. The P wave was first flattened and then gradually disappeared. But only PR and QT interval were prolonged slightly. No significant change in QRS complex was observed at related therapeutic concentrations. *In vivo* and *in vitro* experiments revealed that Tet could decrease the heart rate. This may result from a long-

term protection of the myocardium through a decrease in oxygen consumption, which is one of the therapeutic goals for treatment of some cardiovascular disorders.

Surface electrogram and action potentials The normal developed tension and surface electrogram were recorded simultaneously^[25]. Sixty minutes after administration of Tet 32 $\mu\text{mol/L}$, the normal developed tension (contractile force) was decreased distinctly. But the amplitude and duration of the R wave remained unchanged. It indicated that Tet produced excitation-contraction uncoupling.

Standard microelectrode technique was used to investigate the effect of Tet on the action potential of isolated guinea pig papillary muscles in normal and K^+ -rich Tyrode's solution. Intracellular microelectrode technique and mechano-electric transducer was used to record the action potential and electrically driving contractile force simultaneously. Zong *et al* reported that Tet 1-100 $\mu\text{mol/L}$ produced a concentration-dependent negative inotropic effect and shortened the action potential duration at 20 % and 90 % depolarization, but did not affect resting potential or action potential amplitude, suggesting an effect on excitation-contraction uncoupling^[26].

In high K^+ solutions, which inactivated fast Na^+ channels, Tet 10-100 $\mu\text{mol/L}$ inhibited contractile force, exerted resting as well as frequency-dependent blockage of the maximal upstroke velocity, and decreased action potential amplitude (from 82 mV to 38 mV) as well as resting potential (from -84 mV to -60 mV)^[27]. All these demonstrated its Ca^{2+} channel blocking activity. Similar phenomena were observed in rat cardiomyocytes.

In rabbit sino-atrial node dominant pacemaker cells^[28], Tet 1-100 $\mu\text{mol/L}$ decreased APA, maximal upstroke velocity (V_{\max}), and spontaneously depolarizing velocity of phase 4 (SP_4); and prolonged the sinus circle length (SCL) in a concentration-dependent manner. I_{Ca} (L and T) are considered to contribute to the slow diastolic depolarization of SA nodal cells^[29]. These effects were attributed to its ability in inhibiting I_{Ca} .

Calcium currents Cardiac $I_{\text{Ca-L}}$ and $I_{\text{Ca-T}}$ channels are believed to have different functions. The $I_{\text{Ca-T}}$ is well suited for a role in pacemaker and has been considered to play an important role in late phase 4 depolarization, while the $I_{\text{Ca-L}}$ may contribute to cell depolarization and increased cytosolic Ca^{2+} , which can act as a second messenger for intracellular chemical

signals. Tet inhibits the I_{Ca-L} and reduces Ca^{2+} flows into the cytosol; therefore, the action potential is shortened and the contractility of the heart is decreased. Subsequently the effects of Tet on I_{Ca-T} and I_{Ca-L} were further investigated.

The effect of Tet on slowing inward current in canine cardiac Purkinje fibers was studied by using two-microelectrode voltage clamp technique. The results showed that Tet inhibited the peak value of the slow inwardly current (I_{si} PV) in a concentration- and time-dependent manner. After pretreatment with Tet 30 and 100 $\mu\text{mol/L}$ for 10 min respectively, the I_{si} PV decreased from (48 ± 6) and (38 ± 22) nA to (22 ± 8) nA and (6 ± 8) nA, respectively, which suggested that Tet was a slow channel blocker^[30].

Whole-cell patch-clamp experiments were performed on isolated single ventricular myocytes of guinea pig. Under the current clamp mode, action potentials were recorded at current stimulation of 0.5 Hz, 3 ms. Tet 30 $\mu\text{mol/L}$ greatly shortened APD_{50} and APD_{90} , while affecting neither resting membrane potential nor amplitude of the action potential^[31]. The obtained results of Tet on action potential in isolated single ventricular myocytes were consistent with those of papillary muscles of guinea pig.

Whole-cell patch-clamp technique with or without β -escin-perforated^[32] was performed to examine the effects of Tet on L-type calcium current (I_{Ca-L}) and T-type calcium current (I_{Ca-T}) in isolated single ventricular myocytes of guinea pig.

Calcium currents were separated into T-type and L-type components by different holding potentials (-80 and -40 mV). When a holding potential was -40 mV (most T channels inactivated), depolarizing to 0 mV for 150 ms, a L-type calcium current was elicited. Tet (1-300 $\mu\text{mol/L}$) inhibited L-type calcium current in a concentration-dependent manner with IC_{50} of 14.8 $\mu\text{mol/L}$. The shape of the $I-V$ curve remained similar before and after administration.

From a holding potential of -80 mV, depolarizing to -35 mV for 150 ms T-type calcium currents were evoked. Tet 3, 30, and 300 $\mu\text{mol/L}$ suppressed the I_{Ca-T} in concentration-dependent manner with inhibition rate of $(16.2\% \pm 4.8\%)$, $(39.8\% \pm 7.4\%)$, and $(74.8\% \pm 10.8\%)$, respectively. The inhibitory action of Tet on the I_{Ca-T} may also account for the anti-arrhythmic effect observed by other investigators.

The effects of Tet on both I_{Ca-L} and I_{Ca-T} were investigated in primary cultured neonatal rat ventricular

cells^[33]. Tet produced a significant reduction in L-type calcium current amplitude but did not shift the $I-V$ relationship curve. The IC_{50} of Tet was 0.33 $\mu\text{mol/L}$.

Nifedipine 10 $\mu\text{mol/L}$ was added to abolish the I_{Ca-L} . After administration of Tet, the I_{Ca-T} was reduced by almost 40%. The inhibitory effect of Tet on the I_{Ca-T} ($46\% \pm 12\%$) was less than that on I_{Ca-L} ($56\% \pm 5\%$). These data clearly demonstrated that in neonatal ventricular cells Tet inhibited both T- and L-Type calcium channel currents in a concentration-dependent manner.

T-type Ca^{2+} channels have properties different from those of the L-type and are involved in cardiac pacemaking and regulation of blood flow^[34]. T-channel-selective calcium channel blocker included a number of agents, for example, nifedipine, amiloride, efonidipine, ethosuximide, tetrandrine, mibefradil, *etc*, of which mibefradil is most studied. Mibefradil, an effective anti-hypertensive, anti-anginal, and anti-ischemic agent, has been shown to be beneficial to adjunct therapy in chronic heart failure (CHF)^[35], attenuate leukocyte adhesion, and exert anti-inflammatory effects^[36]. However current clinical and experimental studies showed that mibefradil was withdrawn by the manufacturer because of drug interaction with the cytochrome P-450 3A4 enzyme^[37,38].

Clinical research Early clinical study reported that Tet could relieve angina and hypertension, *etc*. In patients with paroxysmal supraventricular tachycardia, Tet 3-4 mg/kg prolonged sinus cycle length, Atrio-His (A-H) interval, and Atrio-ventricular node effective refractory period, with no change in P-A, His-Ventricular (H-V), QRS, or Q-T intervals. Sinoatrial conduction time and sinus node recovery time were not altered^[39]. These findings may explain the action of Tet in abolishing the reentry to paroxysmal supraventricular tachycardia.

EFFECTS ON VASCULAR SMOOTH MUSCLE CELLS AND ENDOTHELIAL CELLS

Vascular smooth muscle cells The patch-clamp technique was also used to investigate the effect of Tet on voltage-dependent Ca^{2+} channel current in vascular smooth muscle cells isolated from the rat tail artery. The I_{Ca-L} was activated at -20 mV, and the peak value occurred at +10 mV. Tet 10 $\mu\text{mol/L}$ produced a significant reduction in Ca^{2+} current amplitude, but voltage-dependence of current activation was not altered^[40]. It suggested that Tet could inhibit Ca^{2+} influx through Ca^{2+} channels.

The nystatin-perforated whole-cell voltage-clamp technique was employed to examine the effects of Tet on I_{Ca-L} in cultured rat aortic smooth muscle cells^[41]. Tet 1-100 $\mu\text{mol/L}$ reversibly inhibited L-type voltage-dependent Ca^{2+} current in a concentration-dependent manner with IC_{50} value of 5 $\mu\text{mol/L}$ and did not cause any change in the overall shape of the current-voltage relationship of I_{Ca-L} . Inhibitory effects of Tet on I_{Ca-L} exhibited tonic and use-dependent characteristics. These results indicated that Tet directly inhibited the voltage-dependent L-type Ca^{2+} current in vascular smooth muscle cells, which may predominantly contribute to the vasodilatory actions of Tet.

Vascular endothelial cells The effects of Tet on I_{Ca-L} in cultured single bovine pulmonary artery endothelial cells (BPAEC) were examined. BPAEC exhibited strong inward-rectifying K^+ currents upon hyperpolarizing voltage steps, with a reverse potential near at -70 mV. Small outward K^+ currents dependent on the presence of Ca^{2+} in the pipette can be stimulated in BPAEC by depolarizing voltage steps. Addition of thapsigargin 100 nmol/L caused a significant enhancement of depolarization to evoke Ca^{2+} -dependent outward K^+ current, which could also be abolished by Tet 30 $\mu\text{mol/L}$. But Tet itself depressed neither outward K^+ nor inward-rectifying K^+ currents. The results implied that Tet acted by inhibiting the cation channel characteristic of Ca^{2+} release-activated Ca^{2+} channel present in BPAEC^[18,42]. Tet, in addition with its known inhibitory effects on vascular smooth muscle by virtue of its Ca^{2+} antagonistic actions, also inhibited Ca^{2+} release-activated Ca^{2+} channels in vascular endothelial cells

In endothelial cell line (HUV-EC-C) originally derived from human umbilical vein^[17], Tet 0.5-50 $\mu\text{mol/L}$ reversibly decreased the amplitude of K^+ outward current, which was believed to be Ca^{2+} -activated K^+ current. The IC_{50} value was 5 $\mu\text{mol/L}$. In outside-out configuration, Tet 5 $\mu\text{mol/L}$ did not change the single-channel conductance but significantly reduced the opening probability of large conductance of Ca^{2+} -activated K^+ (BK_{Ca}) channel. The change in the kinetic behavior of BK_{Ca} channel by Tet is due to a decrease in mean open time and an increase in mean closed time. The direct inhibition of BK_{Ca} channels by Tet should contribute to its effect on the functional activities of endothelial cells.

The non-selection cation channels existing in endothelial cells are involved in the regulation of intracellular Ca^{2+} concentration and in the control of the activity

of BK_{Ca} channel. The blockade of BK_{Ca} channels may cause membrane depolarization and vasoconstriction. Tet at therapeutically relevant concentrations can directly inhibit the activity of BK_{Ca} channels in HUV-EC-C, which contribute to vasoconstriction of microvascular wall.

Tet exerted dual effects on vascular reactivity. As a vasodilator, it acted directly on the smooth muscle cells and as a vasoconstrictor it acted via the endothelial cells.

CONCLUSION

In past decade, Tet attracted more attention for its potential as a Ca^{2+} channel blocker. According to our data and others reports, Tet can block multiple ion channels, such as L-type, T-type calcium channels, BK_{Ca} , and Ca^{2+} release-activated Ca^{2+} channels, *etc*. Its cardiovascular effects may particularly be related with its blockage on L-type calcium channels. Tet has been shown its value in the clinical treatment of a wide range of cardiovascular disorders.

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