Cardiovascular pharmacological effects of bisbenzylisoquinoline alkaloid derivatives[1]

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ABSTRACT

Tetrandrine, dauricine, daurisoline and neferine are bisbenzylisoquinoline alkaloid derivatives isolated from Chinese traditional medicine and herbs. The cardiovascular pharmacological effects and the mechanism of actions of these compounds were reviewed. Tetrandrine isolated from *Stephania tetrandra* S Moore possesses antihypertensive and antiarrhythmic effects. The antihypertensive effects of tetrandrine have been demonstrated in experimental hypertensive animals and in hypertensive patients. Recent studies showed that in addition to its calcium antagonistic effect, tetrandrine interacted with M receptors. Modulation by M receptor is one of the pharmacological mechanisms of cardiovascular effects of tetrandrine. Dauricine and daurisoloine were isolated from *Menispermum dauricum* DC. The antiarrhythmic effects of dauricine have been verified in different experimental arrhythmic models and in cardiac arrhythmic patients. Dauricine blocked the cardiac transmembrane Na^+, K^+ and Ca^{2+} ion currents. Differing from quinidine and sotalol, which exhibited reverse use-dependent effect, dauricine prolonged APD in a normal use-dependent manner in experimental studies. The antiarrhythmic effect of daurisoline and neferine which is an alkaloid isolated from *Nelumbo nucifera* Gaertn, and their mechanisms of actions have also been studied. The antiarrhythmic effect of daurisoline is more potent than that of dauricine.

INTRODUCTION

Tetrandrine, dauricine, daurisoline, and neferine are bisbenzylisoquinoline alkaloid derivatives isolated from Chinese traditional medicine and herbs. Tetrandrine (Tet) was isolated from the roots of *Stephania tetrandra* S Moore. As early as in the middle of twentieth century, Tet has already been the target of the pharmacological research work in our university. Tet has been used for the treatment of hypertension and silicosis in China. Dauricine (Dau) and daurisoline (DS) were isolated from rhizome of *Menispermum dauricum* DC. The antiarrhythmic effects of Dau have been verified in experimental animal studies and in patients with cardiac arrhythmias. Neferine (Nef) was isolated from the seed embryo of *Nelumbo nucifera* Gaertn. It has also been demonstrated that Nef possesses antiarrhythmic action. In the past few decades, tremendous amount of work have been done to explore the pharmacological effects and the mechanism of actions of these compounds. The aim of the present review is to summarize and review the cardiovascular pharmacological effects and the mechanisms of actions of these compounds. Most of
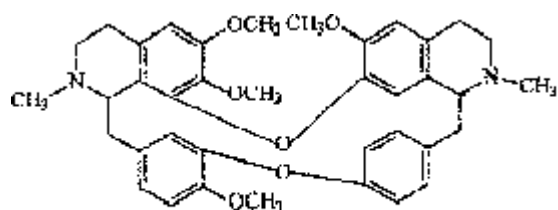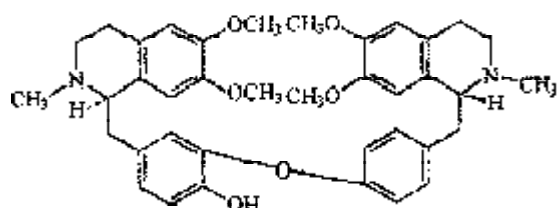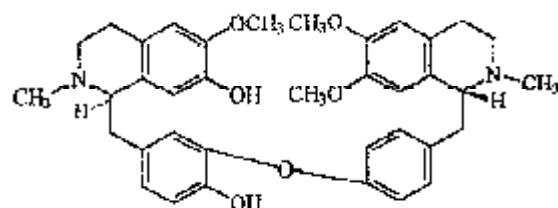
these studies cited here were mainly conducted in the Faculty of Pharmacology of our University.
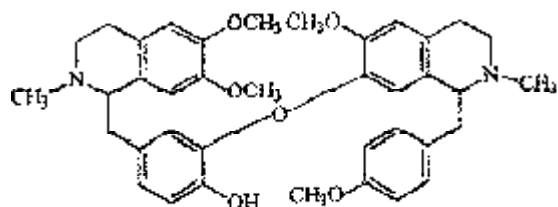

Tetrandrine

Daurisine

Daurisoline

Neferine

TETRANDRINE (TET)

It has been demonstrated that Tet possesses anti-arrhythmic action in several experimental arrhythmic models[1,2], antihypertensive effect in spontaneously hypertensive rats, renal hypertensive rats and Doca-salt hypertensive rats[3]. It also has been demonstrated that Tet is a calcium antagonist of Chinese medicine origin[4,5]; is not a selective calcium channel blocker in vascular smooth muscle[6]. The mechanism of actions of Tet has been extensively explored. Tet could inhibit both T and L type calcium channels currents in ventricular cells[7]; block voltage-dependent Ca^{2+} and Ca^{2+} activated K^+ channels[8]. In radioligand binding study of rat brain membranes preparation, Tet displayed high

affinity for M receptors[9]. Tet acted as an allosteric modulator for M receptor, and showed high affinity with m_1, m_2 receptor subtype expressed in baculovirus infected insect cells (*Spodoptera frugiperda*, Sf9)[10]. The mAChR subtypes expressed in Sf9 cells had essentially the same specificity for subtype-specific ligands as mAChR subtype in mammalian tissues[10]. By using electrophysiological methods and selective antagonists for M receptor subtypes (M_1: pirenzepine; M_2: AF-DX 116; M_3: 4-DAMP), recently the influence of selective antagonists for M receptor subtypes on the cardiovascular effects of Tet was investigated.

Modulation by muscarinic receptor antagonists on negative chronotropic effects of tetrandrine To investigate the influence of selective antagonist for M receptor subtype on Tet's effect of reducing heart rate and inhibiting sinoatrial node (SAN) function and its ionic mechanism, the effects of reducing heart rate of Tet were maintained in isolated right atrium and pithed rats; modification on action potentials (AP) of SAN cells and L-type calcium current (I_{Ca-L}) by Tet were recorded by means of standard microelectrode and patch-clamp whole cell recording techniques. The results showed that Tet inhibited spontaneous beating rate of isolated right atrium (EC$_{50}$ value=23.7 μmol/L) and reduced heart rates in pithed rats in a concentration dependent manner (EC$_{50}$ value=18.6 mg/kg).

Automaticity of SAN was inhibited by Tet. AP upstroke velocity (V_{max}), spontaneous depolarization rates in phase 4 (SP$_4$) were decreased and sinus cycle length (SCL) was prolonged when treated with Tet. Tet (30 μmol/L) caused a reduction in peak value of I_{Ca-L} from (1275±190) pA to (498±94) pA in isolated single cardiomyocyte. Atropine and AF-DX 116 (M$_2$ subtype selective antagonist) could attenuate such effects of Tet in a competitive mode. The results suggest that negative chronotropic effects of Tet are due to its inhibition of I_{Ca-L}. Modification on I_{Ca-L} is the major mechanism of M receptor modulating Tet effects[11].

Modulation by muscarinic receptor antagonists on negative inotropic effect of tetrandrine The influence of M receptor antagonists on negative inotropic effects of tetrandrine has also been studied. In isolated guinea pig left atrium, atropine (0.03 μmol/L) and AF-DX 116 (1 μmol/L) markedly inhibited Tet's effect of decreasing contracting force, EC$_{50}$ value (μmol/L) changed from (28.9±0.9) to (125±21) and (127±13) respectively. Atropine (0.03 μmol/L) partially antagonized shortening effects of Tet on action potential dura-

tion at 20 % (APD_{20}) and action potential duration at 50 % (APD_{50}) in rabbit right atrium, but did not affect prolongation of action potential duration at 90 % (APD_{90}) in high concentration of Tet. In single isolated guinea pig ventricular cells, Tet could inhibit I_{Ca-L}; inhibit inwardly rectifier potassium current (I_{k1}), but the inhibitory effect of Tet (30 μmol/L) on I_{k1} was not affected by aropine (1 μmol/L), while reversed by acetylcholine (1 μmol/L). The results also suggest that modulation of M receptor antagonist on calcium channel blocking effects of Tet is its main ionic mechanism in attenuating negative inotropic effects of Tet[12].

Modulation by atropine on relaxant effects of Tet in isolated rabbit aorta The relaxant effect of Tet was determined in rabbit aortic preparations. Tet caused concentration-dependent relaxation in phenylephrine or KCl induced contraction with similar maximal responses. The relaxant effect was not endothelium-dependent and pretreatment with atropine (0.1 μmol/L) had no influence on it[13].

Beneficial effects of tetrandrine on functional recovery after ischemia and reperfusion in isolarted-working hearts of guinea pigs[14] It has been suggested that acetylcholine is an endogenous myocardial protective agent[15]. The protective effect involves the mechanism of muscarinic stimulation. By using the model of ischemia-reperfusion injury in isolated working heart of guinea pig, the change of cardiac function after treatment with Tet was investigated. It was found that both methacholine and Tet were able to ameliorate the ischemia-reperfusion injury of the heart and promote the recovery of cardiac functions. Muscarinic antagonist atropine could almost abolish such protective effects. It is suggested that the protective effect of tetrandrine is not only due to its calcium channel blockade, but also involves the mechanism of M receptor stimulation.

Influence of tetrandrine on cardiovascular response modulated by muscarinic receptor subtypes To get more information of the action mode of interaction between Tet and cardiovascular M receptor subtypes, the influence of Tet on different responses induced by stimulation of distinct M receptor subtypes was studied in anesthetized and pithed rats and compared with classical calcium channel blocker verapamil. Methacholine caused hypotensive and bradyrhythmic effects in both normotensive rats (NTR) and renal hypertensive rats (RHR) by activating M_3 and M_2 receptor, while activation of M_1 receptor in the sympathetic gan-

glia caused pressor response in pithed rats. Tet could strengthen the effects of methacholine in anesthetized rats (NTR and RHR). In pithed rats, Tet shifted the dose-response curve of hypotensive activity of methacholine toward left in low concentration of methacholine, while in high concentration of methacoline the curve was shifted to right. Tet acted like a partial agonist. But Tet antagonized the pressor effect mediated by the stimulation of M_1 receptor in pithed rats. The pK_B value for Tet was 8.69 (M_1), 8.63 (M_2) and14.45 (M_3). Tet shows different selectivity for M receptor subtypes. It is more selective for M_1 and M_2 subtypes. Verapamil could antagonize the effects induced by the stimulation of M_1, M_2, and M_3 receptors. Verapamil has anticholinergic effects[13].

The results mentioned above confirm the hypothesis that Tet interacts with cardiovascular muscarinic receptor. Tet shows the property of a partial agonist of M receptor and modulation by M receptor is one of the pharmacological mechanisms of cardiovascular effects of tetrandrine, also it is more selective to M_1 and M_2 receptors but not M_3 subtype.

DAURICINE (DAU) AND DAURISOLINE (DS)

We have also devoted to study the antiarrhythmic effects and to explain the mechanism of actions of Dau and DS.

Antiarrhythmic effects of daurcine The antiarrhythmic effects of Dau have been demonstrated in several experimental arrhythmic models and in clinic[2,16,17]. In isolated guinea pig atria and papillary muscle, Dau (0.1 mmol/L) reduced the force of contraction and decreased the amplitude and V_{max} of action potential. Dau (1-300 μmol/L) increased the duration of action potential (APD) and the functional refractory period. The effect of acetylcholine (30 μmol/L) in shortening the APD of the left atria was antagonized by Dau (30 μmol/L)[18]. Dau (20 μmol/L) prolonged APD_{90} in a use-dependent manner in guinea pig papillary muscles. Dau became more effective in lengthening at short cycle length, whereas quinidine (1 μmol/L) and sotalol (10 μmol/L) were less effective in lengthening APD at short cycle lengths. The effects of quinidine and sotalol on APD exhibited reverse use-dependence. The results indicate that Dau may become the 'ideal' antiarrhythmic drugs[19]. The effects of Dau (40 μmol/L) on the slow action potentials induced by high K^+ (24 mmol/L) in guinea pig papillary muscles and in sinoatrial node cells of rabbit were studied. Dau decreased the maxi-

mal upstroke velocity (V_{max}) of slow action potentials and prolonged the APD_{50}. Bay K8644 (50 nmol/L) (a calcium channel activator) increased the amplitude and V_{max} of slow action potentials, which were antagonized by Dau. An inhibitory influence of Dau on the action potential amplitude (APA) was also observed in papillary muscles superfused with Tyrode's solution containing high K^+ and in rabbit sinoatrial node cells. The results suggest that Dau possesses calcium-antagonistic effect[20].

In human atrial fibers and rabbit atrioventricular node cells, Dau also produced concentration-dependent depression on the APA, Vmax and spontaneous action potential. Dau markedly increased sinoatrial node conduction time (SACT) of the anesthetized rabbits. The results suggest that Dau significantly depressed the sinoatrial node conduction function, and the action potential of the atrial fibers and atrioventricular node cells, which might be related to its antagonizing effect on supraventricular arrhythmias[21].

In the isolated canine cardiac Purkinje fibers, Dau (1-30 μmol/L) inhibited APA, V_{max}, maximal diastolic potentials (MDP) in concentration-dependent manner, and prolongations of APD_{50}, APD_{90} as well as ERP. The automaticity and excitation were significantly reduced at concentration of Dau 30 μmol/L. Dau prolonged APD at fast rate and at slow rate to a similar extent in canine Purkinje fibers, the effect of Dau on APD like aminodarone[22].

By using intracellular microelectrode method to record action potential, the effects of Dau on early afterdepolarizations (EADs) and triggered activity (TA) induced by quinidine in guinea pig papillary muscles were studied. Dau (20 μmol/L) could inhibit EADs and TA induced by quinidine[23]. Dau also exerted an antagonistic action to delay afterdepolarizations (DADs) induced by many inducers such as phenylephrine, isoprenaline, ouabain and caffeine in guinea pig papillary muscle[24]. The results indicate that Dau could inhibit EADs and DADs-induced arrhythmias *in vitro*. To study the effect of Dau on CsCl-induced EADs and ventricular arrhythmias in rabbits (*in vivo*), monophasic action potentials (MAP) of the left ventricle of the rabbit heart *in situ* were recorded with MAP recording technique. CsCl was used to induce EAD and ventricular arrhythmias. Dau could also suppress CsCl-induced EADs and TA in rabbit heart *in vivo*[25].

Ionic mechanisms of antiarrhythmic effects of dauricine By means of intracellular microelectrode and single sucrose gap voltage clamp technique, the effect of Dau on the action potential, the slow action potential (SAP), and slow inward currents (I_{si}) of guinea pig ventricular papillary muscles were observed. Dau prolonged APD, effective refractory period (ERP), significantly decreased APA, V_{max}, and overshot (OS), greatly diminished APA and OS of SAP induced by isoprenaline, and remarkably inhibited Isi. The results suggest that Dau exerted an inhibitory effect on Na^+, Ca^{2+}, and K^+ channels[26].

The effect of Dau on L-type calcium current (I_{Ca}) in guinea pig ventricular myocytes was studied by using whole-cell patch clamp recording method in single ventricular cell of guinea pig. Dau 1, 10, and 100 μmol/L markedly reduced I_{Ca}. Dau inhibited I_{Ca} at 3 Hz and 1 Hz to a similar extent. The results indicate that Dau possesses calcium channel blocking effect and its effect on I_{Ca} appears to be not frequency-dependent[27].

By using voltage clamp technique, it was demonstrated that Dau could inhibit sodium ion current in cardiac Purkinje fibers[28]. Quantitative studies on kinetics of cardiac sodium channels blocked by Dau based on the model of gate-related receptor hypothesis were performed by using computer simulation. The results suggest that binding site of Dau in cardiac sodium channel is activation gate-related receptor site[29].

By using the whole cell configuration of the patch-clamp technique, the inhibitory effects of Dau on potassium currents were investigated in guinea pig ventricular myocytes. Dau (1-100 μmol/L) blocked the rapidly activating component (I_{kr}) and the slowly activating component (I_{ks}) of the delayed rectifier potassium current, as well as reducing I_{kr} and I_{ks} tail currents in concentration-dependent manner. Dau (20 μmol/L) also inhibited the inward rectifier potassium current (I_{k1}). Dau had different characteristics in blocking I_{kr} and I_{ks} from those of quinidine and dofetilide. It did not affect the process of I_{kr} and I_{ks} deactivation. Dau prolonged APD in a use-dependent manner. The effects of Dau on I_{kr} and I_{ks} were similar to that of amiodarone, propafenone, and azimilide[30]. These characteristics of Dau, along with its blockage on L-type calcium current, raises the possibility that this compound will provide effective antiarrhythmic therapy, while minimizing the risk of *Torsades de pointes*.

Effects of dauricine on acute myocardial infarction In four kinds of isolated vascular smooth muscle preparations, Dau relaxed the vascular smooth muscles. In isolated rat hearts, Dau increased coro-

nary arterial flow, inhibited myocardial contraction force and slowed down the heart rate. By using the ^{86}RbCl-extraction method Dau increased the myocardial blood flow of mice. Dau reduced the myocardial infarct size at 24 h after acute coronary occlusion in rats, inhibited the thromboxane A$_2$ (TXA$_2$) formation and platelet aggregation[31-35]. In anesthetizd dogs Dau exerted protective and anti-arrhythmic effects on acute myocardial infarction. Dau depressed the elevated coronary venous blood lactate dehydrogenase (LDH) and creatine phosphate kinase (CPK) after left anterior descending coronary artery (LAD) occlusion. Dau produced antagonistic effects on acute myocardial ischemia-induced ventricular ectopic activities (VE) and ventricular tachycardia (VT). Ventricular fibrillation (VF) is tended to descend[36].

It is possible that Dau exerted its protective effect on acute myocardial ischemia by inhibiting calcium influx across the myocardial membrane and by limiting the intracellular calcium overload, decreasing the myocardial O$_2$ consumption, increasing the coronary blood flow, improving the myocardial blood supply, and inhibiting the TXA$_2$ formation and platelet aggregation.

Antiarrhythmic effect of daurisoline (DS) DS is a same kind of phenolic alkaloid as Dau isolated from *Menispermum dauricum* DC. The antiarrhythmic effect of DS has also been demonstrated in several experimental arrhythmic models. DS had similar antiarrhythmic effects with Dau, but its antiarrhythmic effects were more potent than that of Dau[37].

It prolonged APD with a normal use-dependent manner in guinea pig papillary muscles *in vitro*[38]. The effect of DS on monophasic action potential (MAP) of rabbit hearts *in vivo* has been studied with MAP recording technique. The results showed that DS decreased monophasic action potential amplitude (MAPA) and prolonged monophasic action potential duration at 50 % and 90 % (MAPD$_{50}$, MAPD$_{90}$), and ERP. DS had no reverse frequency-dependent effect[39]. It suggests that DS may be a potential antiarrhythmic drug in further clinical use.

By using Ca^{2+} sensitive microelectrode technique to record intracellular Ca^{2+} activity (a$^i_{Ca}$) and triggered activity (TA) arising from delayed afterdepolarization (DAD) in myocardium, the effect and the mechanism of DS on DAD was investigated. Strophantin G (3 µmol/L) yielded an increase in resting myocardial a$^i_{Ca}$ and transient elevations of a$^i_{Ca}$ during the development of DAD and TA. By treatment with DS or verapamil,

strophantin G-caused elevations of the a$^i_{Ca}$ in resting and provoked myocardium were eliminated and TA disappeared. DS (50 µmol/L) reduced Na$^+$-free medium-induced elevation of dog Purkinje fibers a$^i_{Ca}$ and abolished caffeine-induced increase of dog myocardial a$^i_{Ca}$. It is concluded that DS inhibited DAD and TA by preventing an increase of a$^i_{Ca}$ via transmembrane Ca^{2+} entry and Ca^{2+} release from the reticulum[40].

NEFERINE (NEF) The antiarrhythmic effects of Nef have also been demonstrated in several different experimental studies[41]. The effects of Nef on the electrical and mechanical activity were investigated in guinea pig papillary muscles and atria. Nef 0.1 mmol/L reduced the force of contraction, decreased the amplitude and V_{max} of action potential (AP), prolonged the APD$_{50}$, APD$_{90}$ and ERP. The effect of acetylcholine 10 µmol/L which shortened the APD of the left atria was partly antagonized by Nef 30 µmol/L[42]. Nef 30 µmol/L decreased the automaticity-inducing effect of adrenaline in guinea pig atria. Nef 30 µmol/L suppressed and shifted the isoprenaline dose-effect curve to the right non-parallel, an action different from the action of propranolol. The effect of Nef on the dose-response curves of Ca^{2+} was studied in left atria of guinea pigs. Nef, as verapamil, showed dualistic action in Ca^{2+}-antagonism[43].

Nef also suppressed the contractility of the rabbit papillary muscles, prolonged functional refractory period (FRP), inhibited automaticity, positive staircase and post rest potentiation. The results of Nef can be explained by a non-specific inhibition of the current of Na$^+$, Ca^{2+} and K$^+$. Its antagonistic efficiency to arrhythmias may be related to these effects[44].

By using turbidimetry and Fura-2 fluorescence technique, the effect of Nef on platelet aggregation and concentration of cytoplasmic free calcium ([Ca^{2+}]$_i$) were studied in human and rats. Nef could dose-dependently inhibit human or rat platelet aggregation induced by ADP, collagen and epinephrine both *in vitro* and *ex vivo*. In the presence or absence of external Ca^{2+}, Nef inhibited ADP-stimulated increase of [Ca^{2+}]$_i$, but had no effect on resting [Ca^{2+}]$_i$. The results suggest that Nef not only decreased Ca^{2+} influx but also inhibited internal Ca^{2+} discharge[45].

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