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Cardiovascular Actions of Berberine

Chi-Wai Lau, Xiao-Qiang Yao, Zhen-Yu Chen,*
Wing-Hung Ko, and Yu Huang

*Departments of Physiology and *Biochemistry,*
Chinese University of Hong Kong, Shatin, Hong Kong, China

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ABSTRACT

Berberine, is an alkaloid from *Hydrastis canadensis* L., Chinese herb Huanglian, and many other plants. It is widely used in traditional Chinese medicine as an antimicrobial in the treatment of dysentery and infectious diarrhea. This manuscript describes cardiovascular effects of berberine and its derivatives, tetrahydroberberine and 8-oxoberberine. Berberine has positive inotropic, negative chronotropic, antiarrhythmic, and vasodilator properties. Both derivatives of berberine have antiarrhythmic activity. Some of cardiovascular effects of berberine and its derivatives are attributed to the blockade of K^+ channels (delayed rectifier and K_{ATP}) and stimulation of Na^+–Ca^{2+} exchanger. Berberine has been shown to prolong the duration of ventricular action potential. Its vasodilator activity has been attributed to multiple cellular mechanisms. The cardiovascular effects of berberine suggest its possible clinical usefulness in the treatment of arrhythmias and/or heart failure.

INTRODUCTION

Berberine, an alkaloid isolated from *Hydrastis canadensis*, the Chinese herb Huanglian, and many other plants, such as the Berberidaceae and Ranunculaceae families, has a long history in traditional Chinese medicine. Berberine is present in roots, rhizomes, and stem bulk of the plants. The chemical name of berberine is 5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-α]quinolizinium. Various pharmacological actions, including antibiotic (1,15), immunostimulant (35), antitumor (33), and antimotility prop-

Address correspondence and reprint requests to: Yu Huang, PhD, Department of Physiology, Chinese University of Hong Kong, Shatin, Hong Kong, China.
Tel: +852 2609-6787; Fax: +852 2603-5022; E-mail: yu-huang@cuhk.edu.hk.

erties (14,52), have been described for berberine. A broad spectrum of antimicrobial activity has made extract of berberine-containing plants or berberine the most successful folklore remedy in China for centuries to combat dysentery and infectious diarrhea (3). However, only limited information has been published on the possible beneficial effects of berberine and related compounds in the cardiovascular system.

Both clinical trials and animal studies have suggested a number of beneficial effects of berberine on cardiovascular performance. Berberine prevented ischemia-induced ventricular tachyarrhythmias, enhanced force of cardiac contractions, decreased peripheral vascular resistance and blood pressure.

PHARMACOLOGY

Inotropic Effect

Sabir et al. (39) reported that berberine stimulates isolated atrial preparations from rabbits, guinea pigs, and rats. This report provided, however, little insight into the nature of this stimulant effect. A few years later, a strong positive inotropic activity was observed for berberine in dogs (44) and humans (31). It is, therefore, conceivable that, if further studies could demonstrate its safety and efficacy, berberine might be useful in the treatment of congestive heart failure.

By acute infusion at a rate of 0.2 mg/kg/min for 30 min berberine was found to improve hemodynamics in patients with heart failure, who were refractory to digitalis and diuretics. This effect was likely to be due to marked reduction of systemic and pulmonary vascular resistance and of left ventricular end-diastolic pressure (30). Other significant circulatory changes, produced by intravenous berberine, included increases in cardiac index, stroke index, left ventricular ejection fraction as well as in hemodynamic and echocardiographic indices of left ventricular performance. Berberine decreased arteriovenous oxygen difference without any changes in total body oxygen uptake, arterial oxygen tension, or hemoglobin (30).

In open-chest dogs berberine prevented the programmed electrical stimulation-induced ventricular tachycardia and ventricular fibrillation following acute myocardial infarction. Berberine lengthened the QTc interval and the effective refractory period. These data suggest that berberine may be effective in preventing the onset of the reentrant ventricular tachyarrhythmias and sudden coronary death after myocardial ischemic damage (18). Another group studied the effects of berberine in dogs with ischemic left ventricular failure subsequent to ligation of the proximal left anterior descending coronary artery followed by serial occlusions of the distal left circumflex coronary artery. Berberine was administered to these animals by an intravenous bolus injection (1 mg/kg) followed by a constant infusion (0.2 mg/kg/min, for 30 min). The drug increased cardiac output and decreased left ventricular end-diastolic pressure and systemic vascular resistance. The hemodynamic effects were correlated with changes in plasma concentrations of berberine (18). Berberine improved the impaired left ventricular function by its positive inotropic effect and mild systemic vasodilatation.

An extensive study on the effects of berberine in guinea pig atria was published by Shaffer (41). In his experiments berberine had a unique activity profile, producing both positive inotropic and negative chronotropic effects. The positive inotropic effect was ap-

parently not mediated by stimulation of β- or α-adrenoceptors since this effect was unaffected by propranolol or phentolamine. The positive inotropic effect appeared to be caused by enhancement of force-velocity relationship of cardiac myocytes (41). Cardiac glycosides enhance cardiac contractility by inhibiting Na^+–Ca^{2+} exchanger via suppression of Na^+–K^+-ATPase (11). However, the positive inotropic effect of berberine is unlikely to be due to inhibition of Na^+–K^+-ATPase, since berberine, at 100 μM, had no effect on the activity of guinea pig brain Na^+–K^+-ATPase (10). Berberine inhibited cardiac phosphodiesterase with an IC_{50} value of 692 μM (10). However, the concentration of berberine required for this action is 6 to 60 times higher than that required for its positive inotropic effect. It was suggested that berberine may alter the availability of the intracellular calcium pool related to beat-to-beat control of contractility (41). This intriguing hypothesis has never been further investigated.

A striking electrophysiological action of berberine and its derivatives on cardiac myocytes is lengthening of action potential without affecting other action potential characteristics. This effect was observed in various species including rats (6), guinea pigs (46), rabbits (37), cats (40), dogs (37), and humans (6). Selective lengthening of action potential duration would increase Ca^{2+} influx through the transmembrane Ca^{2+} channels, elevate Ca^{2+} mobilization from the sarcoplasmic reticulum and rise cytostolic free Ca^{2+} concentration required for enhanced cardiac contractility.

Berberine (3–30 μM) produced a significant prolongation of action potential duration in isolated guinea pig ventricular fibers without effecting the resting membrane potential and action potential amplitude. This effect may be partially due to inhibition of the delayed rectifier K^+ current, which contributes towards the repolarizing phase of the ventricular action potential and is partly due to stimulation of Ni^{2+}-sensitive Na^+–Ca^{2+} exchanger current. In contrast, berberine has no effect on inwardly rectifier K^+ channels (46). The similar K^+ channel blocking action was also observed for berberine within the same concentration range (IC_{50} = 4.1 μM) in cat ventricular myocytes (40). There are, however, conflicting reports in the literature on the effect of berberine on cardiac voltage-gated Ca^{2+} currents. Berberine increases or decreases L-type Ca^{2+} currents in guinea pig atrial and ventricular cells (46,50) but has no effect on the high threshold Ca^{2+} current in cat ventricular cells (40).

Antiarrhythmic Effect

Berberine was found to antagonize arrhythmias induced in dogs (28) and rats (36). This action may be attributable to an increase in the effective refractory period of Purkinje fibers (37). It has been suggested that berberine exerts class III antiarrhythmic effects in cardiac muscle of mammals *in vitro* (37). The majority of class III antiarrhythmic drugs act primarily by blocking cardiac delayed rectifier K^+ channels. As a result, a sufficient prolongation of myocardial refractoriness allows the wavelength of activation to exceed the path length of the reentrant circuit, thus preventing the initiation and maintenance of reentrant excitation (12). Delayed afterdepolarization is regarded as one of the important electrophysiological elements for cardiac arrhythmia (21). Berberine was found to suppress the amplitude of delayed afterdepolarization induced by ouabain in isolated guinea pig right ventricular papillary muscle and in rabbit left ventricular muscle *in vivo* (45). Inhibition of Na^+ influx may be the possible underlying mechanism for the reduced am-

plitude of delayed afterdepolarization by berberine. It is considered that a transient inward current carried primarily by Na^+, which is intimately associated with an increase in intracellular Ca^{2+} overload, is responsible for the delayed afterdepolarization. This effect is also likely to be involved in the antiarrhythmic action of berberine.

Cardiac ATP-sensitive K^+ (K_{ATP}) channels could serve as another potential target for the antiarrhythmic activity of berberine. In isolated guinea pig papillary muscles berberine, at 3 μM, significantly inhibited, while at 100 μM completely blocked the shortening of action potential duration and the effective refractory period induced by hypoxia or cromakalim, K_{ATP} channel activator. Hypoxia-induced decrease in cardiac action potential duration is mainly mediated by activation of K_{ATP} channels (32). Patch-clamp data show that berberine (3–100 μM) mimicked the effect of glibenclamide, a potent blocker of K_{ATP} channels, inhibiting both K_{ATP} channel activity and cromakalim-evoked outward K^+ current (45). The blocking effect of berberine on K_{ATP} current is likely to be caused by a reduction of open state probability since berberine had no apparent effect on single channel conductance or the time constant for the open and closed state of the channel (46). The reported beneficial effect of berberine on ischemia-induced arrhythmias can be attributed to inhibition of K_{ATP} channel activation and subsequent shortening of action potential duration and effective refractory period during ischemia.

In a clinical study, Zheng and Zheng (54) reported that berberine might be useful in a long-term therapy of ventricular premature beats. It could conceivably decrease mortality in patients suffering from congestive heart failure. Frequency and complexity of ventricular premature beats were decreased and the left ventricular ejection fraction were increased by berberine at a daily oral dose of 1.2 g for 2 weeks. These changes have been correlated with plasma concentrations of berberine.

Chronotropic Effect

Berberine has negative chronotropic effect on cardiac pacemaker cells. At 10 to 100 μM it decreased the frequency of spontaneous contractions of rabbit sinoatrial cells (37) and guinea pig right atria (41); this effect was concentration-dependent. The decrease in frequency of contractions was accompanied by a depression of the phase 4 depolarization without significant changes in other parameters of the nodal action potential (37). Atropine did not affect the bradycardic effect of berberine in guinea pigs and rabbits (37,41), indicating that muscarinic receptors are not involved. Cholinergic stimulation to the heart is unlikely to be the mechanism underlying the bradycardiac effect, since berberine lowers the heart rate with similar effectiveness in bilaterally vagotomized rats (38). Local anesthetic activity was reported for berberine at higher concentrations (38). The amplitude of action potential in rabbit vagus nerve was not affected by berberine at 500 μM (37). On the other hand, berberine (30 μM) did not alter the positive chronotropic effect of isoproterenol (37).

Cardiac Effect of Berberine Derivatives

Tetrahydroberberine, an analog of berberine, protected rat myocardium from ischemia and reperfusion injury in anesthetized rats; it also reduced infarct size at 4 h after ligation of left anterior descending coronary artery. In hearts, perfused according to Langerdorff,

tetrahydroberberine, 1 to 10 μM, markedly decreased the incidence of ventricular tachycardia and ventricular fibrillation (55). These beneficial cardiac effects of berberine may be related to increased myocardial blood flow and reduced myocardial oxygen consumption (2). These studies suggest that tetrahydroberberine could be useful agent in the treatment of acute myocardial infarction. Even though tetrahydroberberine reduced high K^+-induced contraction and ^{45}Ca influx in isolated rat aorta, this effect was weaker than that of verapamil. It remains to be determined whether tetrahydroberberine, like verapamil, can prevent myocardial damage caused by ischemia and reperfusion (53).

8-Oxoberberine, a derivative of berberine, has been reported to exert antiarrhythmic activity, much like a class III antiarrhythmic agent. 8-Oxoberberine, like berberine, exerted positive inotropic and negative chronotropic actions. In rat left atria 8-oxoberberine, 10 to 100 μM, increased atrial contractility. In spontaneously beating right atria, 8-oxoberberine increased atrial contractility but slightly decreased the rate of contractions. The positive inotropic and the negative chronotropic effects of 8-oxoberberine are not likely to be mediated by autonomic nervous system, since neither prazosin, propranolol, or atropine modified the effects of 8-oxoberberine. The cyclic AMP-dependent pathway is not likely to be involved, since 3-isobutyl-1-methyl-xanthine, an inhibitor of phosphodiesterase, also did not alter the cardiac effects of 8-oxoberberine (6). Patch-clamp study revealed that 8-oxoberberine prolonged the duration of rat atrial action potential; 4-aminopyridine, a blocker of voltage-gated K^+ channels, blunted this effect.

8-Oxoberberine inhibited the integral of the transient outward current (I_{to}) with a KD value of approximately 4 μM in either human or rat atrial myocytes (6). 8-Oxoberberine inhibited I_{to} by binding to open-state channels or by shifting the steady state inactivation curve of I_{to}. The I_{to} blocking potency of 8-oxoberberine was greater than that of dicentrine but similar to that of quinidine (42). In human or rat aorta 8-oxoberberine, like berberine, had no effect on inwardly rectifier K^+ channels (6). In human or rat ventricular myocytes 8-oxoberberine had quinidine-like effects. In addition to prolonging action potential duration, it decreased the maximal rate of action potential upstroke, probably by inhibiting inward Na^+ current (5). This effect, together with K^+ channel blocking action, may be responsible for the antiarrhythmic activity of 8-oxoberberine (Table 1).

TABLE 1. Electrophysiological effects of berberine and its derivatives on cardiac myocytes

	APD	ERP	I_K	I_{IR}	I_{ATP}	I_{Na}	$I_{Ca–L}$
Rat	↑		↓	—			
Guinea pig	↑	↑			↓		↑↓
Rabbit	↑	↑					
Cats	↑		↓	—			—
Dogs	↑	↑					
Human	↑	↑		—			

Abbreviations: APD, action potential duration; ERP, effective refractory period; I_K, delayed rectifier outward K^+ current; I_{IR}, inwardly rectifier K^+ current; I_{ATP}, ATP-sensitive K^+ current; I_{Na}, inward Na^+ current; $I_{Ca\text{-}L}$, L-type voltage-gated Ca^{2+} current.

Vasodilatory and Hypotensive Effects

The early studies showed that intravenously administered berberine transiently lowered blood pressure in dogs (19,20). Berberine, at low concentrations, 2 to 4 μg/mL, increased cardiac contractility and coronary flow with little effect on the heart rate (19). The hypotensive action of berberine has been attributed to its ability to enhance the hypotensive effect of acetylcholine (20). As a short-acting hypotensive agent, berberine may have little clinical potential. However, the interest in the hypotensive activity of berberine was recently renewed, since berberine derivatives (13) or even berberine itself (9) were found to have sustained hypotensive action. Berberine dilated isolated renal blood vessels, prolonged the hypotensive action of vagus nerve stimulation or of acetylcholine, and inhibited carotid sinus pressor reflex (27). In rats the hypotensive effect of berberine is not abolished by vagotomy or by pentolinium-induced ganglionic blockade (9). Chun et al. (9) attributed the acetylcholine-potentiating effect of berberine to its ability to inhibit acetylcholinesterase. However, in nonvascular smooth muscle berberine had an antimuscarinic effects (43).

Both clinical (31) and animal (9) studies demonstrated that berberine prevents ischemia-induced ventricular tachyarrhythmia, stimulates cardiac contractility, and lowers peripheral vascular resistance and blood pressure. Berberine increased coronary blood flow in anesthetized open-chest dogs and in isolated guinea pig hearts with ventricular fibrillation induced by electrical stimulation (16).

The antihypertensive effect of another berberine derivative, 6-protoberberine, has been recently described in conscious spontaneously hypertensive rats (SHRs). 6-Protoberberine lowered systolic blood pressure in a dose-dependent manner. By intracerebroventricular administration to SHRs, 6-protoberberine decreased systolic arterial blood pressure and heart rate (29). The mechanism of hypotensive action of 6-protoberberine is likely to involve a central sympatholytic effect.

Several mechanisms have been proposed to explain the vasodilatory/hypotensive action of berberine and its derivatives. Ko and Lim (24) reported that berberine caused hypotension in rabbits by blocking α-adrenoceptors, but in dogs the hypotensive effect appears to involve a direct vascular action of berberine, that is independent of adrenergic, cholinergic or histaminerigc mechanisms (38). In isolated swine coronary artery strips, berberine competitively inhibited norepinephrine without affecting the maximal contraction (16), suggesting that berberine is an α-adrenoceptor antagonist. Berberine was also reported to possess an antagonistic effect on α-adrenoceptor-mediated contraction of rat or rabbit aorta (34). Tetrahydroprotoberberine, another berberine analog, exerted competitive antagonism at α_1-adrenoceptors in rat aorta and did not relax aortic strips contracted by various constrictors, including the thromboxane A_2 analogue, U46619 (23). However, in a recent study berberine at concentrations higher than 0.1 μM caused a noncompetitive antagonism of phenylephrine-induced contractions of rat mesenteric artery; it relaxed phenylephrine- and U46619-constricted arteries with similar potency (25). This observation did not support α_1-adrenoceptor antagonist action as the principal mechanism of berberine-induced hypotension. The possibility that berberine, at higher concentrations, may prolong the vasoconstrictor effect of norepinephrine by inhibiting degradation of catecholamines cannot be excluded. Berberine competitively inhibited A type monoamine oxidase, prepared from rat brain mitochondria, with an IC_{50} value of 126 μM (26).

The endothelium-dependent component of berberine-induced vasorelaxation was demonstrated on isolated rat and rabbit arteries (7,8,25,48). Endothelial nitric oxide appears to be the primary mediator since inhibition of nitric oxide activity attenuates the berberine-induced relaxation to the same extent as that observed in endothelium-denuded arteries (25). In rat aorta, the relaxant response to low concentrations of berberine (<1 μM) was dependent solely on the presence of endothelium (48). Berberine exerts a relaxant effect on rabbit isolated corpus cavernosum, which is attributable to nitric-oxide-dependent and -independent properties, and intracavernous injection of berberine (3 mg/kg) increases the intracavernous pressure (7). This local penile effect suggests that berberine may have the potential as intracavernous injection therapy for erectile dysfunction. It remains, however, to be determined whether berberine would stimulate nitric oxide release in the endothelial cells.

K^+ channels play an important role in the regulation of muscle contractility and vascular tone. In many instances, vasodilation mediated by membrane hyperpolarization is attributed to a rise in K^+ permeability. Direct activation of K^+ channels in arterial smooth muscle cells normally hyperpolarizes the cell membrane and thus inhibits Ca^{2+} influx through voltage-sensitive Ca^{2+} channels. Two independent recent studies demonstrate that the arterial K^+ channel may be a potential cellular target for the action of berberine (7,25). Berberine-induced relaxation in endothelium-denuded rings was significantly attenuated by putative K^+ channel blockers, such as the tetraethylammonium ions, $BaCl_2$ and 4-aminopyridine in rat mesenteric arteries (25) and by blockers, such as charybdotoxin, in rabbit corpus cavernosal tissue (7). The possible stimulatory effect on K^+ channels may contribute in part to the endothelium-independent vasorelaxation induced by berberine. Nevertheless, further electrophysiological studies are needed to demonstrate this effect of berberine in arterial myocytes.

Berberine, in a concentration-dependent manner, partially relaxed rings of rat mesenteric arteries contracted by high K^+. (25). In contrast, berberine, in the same concentration range, failed to influence high K^+-induced contractions of guinea pig aorta (4) or rabbit corpus cavernosum (7). It is worthwhile to note, that in cultured aortic smooth muscle cell line (A7r5) berberine did not affect intracellular Ca^{2+} concentration that had been previously raised by a high-K^+ solution (25). These data indicate that mechanisms other than inhibition of Ca^{2+} channels may underlie the endothelium-independent relaxant response to berberine. However, berberine was reported to inhibit both L- and T-type voltage-gated Ca^{2+} currents in guinea pig ventricular myocytes (50). Alternatively, the effect of berberine on Ca^{2+} channel may be tissue-dependent.

Contradictory data have been published on the effect of berberine on intracellular Ca^{2+}-mediated contractile response in different arterial tissues (4,8). Berberine was reported to abolish caffeine-induced transient contraction in rat arteries (8,25) but not in guinea pig aorta (4). Ca^{2+} from intracellular sources plays usually only a minor role in the agonist-induced sustained tone of blood vessels. The possible inhibition of internal Ca^{2+} release may account, therefore, for only a small part of berberine-induced relaxation. It has yet to be determined whether or not berberine relaxes blood vessels partially by inhibiting vasoconstrictor-induced phospholipase C-mediated production of inositol triphosphate which would reduce intracellular Ca^{2+} mobilization. This is not likely, however, since berberine does not seem to interfere with protein kinase C-mediated contractile pathways in vascular smooth muscle cells (25).

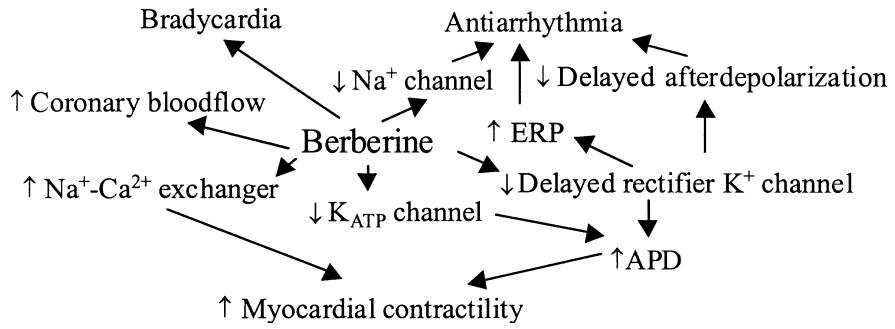

FIG. 1. Proposed mechanisms underlying the cardiac protective effect of berberine and its derivatives with the potential clinical values in the treatment of heart failure and arrhythmias. ADP, action potential duration; ERP, effective refractory period.

Other Effects

Berberine decreased anticoagulant action of heparin in canine and human blood (35). Huang et al. (17) reported a clinical study on berberine-induced inhibition of platelet aggregation. Berberine was found to enhance immunostimulation via increased blood flow to the spleen and to elevate platelet counts in primary or secondary thrombocytopenia (3).

Berberine antagonized cerebral ischemia in rats, probably due to inhibition of ADP-, collagen-, and arachidonic acid-induced platelet aggregation. It also reduced plasma levels of thromboxane B_2 without an obvious effect on the levels of 6-keto-$PGF_{1\alpha}$ (49). Thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ are stable metabolic products of TXA_2 and PGI_2; the former is mainly produced in platelets and latter in endothelial cells. Finally, berberine was recently found to suppress fetal serum-stimulated proliferation of rat aortic smooth muscle cells; it was effective at a concentration range that induces relaxation of rat mesenteric arteries (25). This effect may contribute to a long-term beneficial action of berberine on the vascular system.

CONCLUSION

The potential usefulness of berberine in the therapy of arrhythmias and of heart failure is suggested by multiple cardiovascular actions of berberine. Berberine's antiarrhythmic effect is likely to be mediated by a mechanism involving sequential events, e.g., blockade of delayed rectifier K^+ or K_{ATP} channels, reduction in delayed afterdepolarization, increases in effective refractory period, and resultant prevention of initiation of reentrant excitation in ventricular myocytes. Berberine improves impaired ischemic left ventricular function by positive inotropic effect and mild systemic vasodilatation. Berberine increases myocardial contractility and cardiac output via interrelated mechanisms, including lengthening of ventricular action potential duration due to blockade of K^+ channels, stimulation of Na^+–Ca^{2+} exchanger, and elevation of coronary blood flow (Fig. 1).

The vasodilatory or hypotensive effect of berberine can be attributed to multiple cellular mechanisms such as involvement of endothelial nitric oxide, stimulation of the vascular K^+ channel, inhibition of intracellular Ca^{2+} release, antagonism of α-adrenoceptors

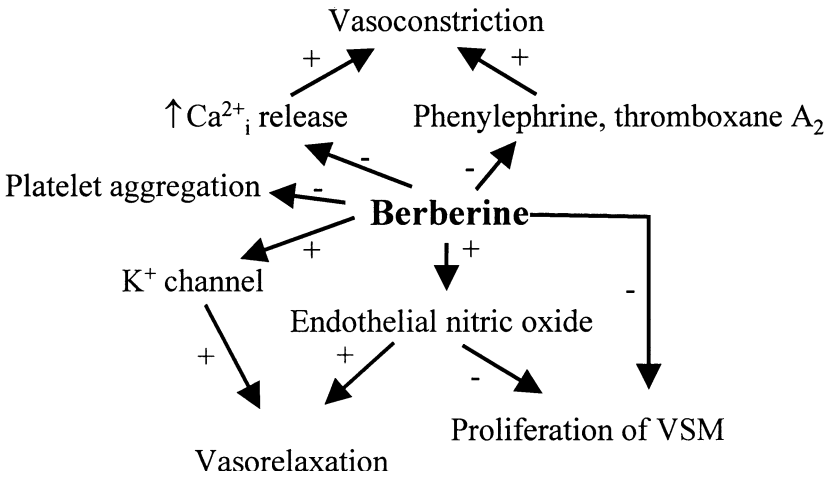

FIG. 2. Pathways mediating the vasodilatory/hypotensive effects of berberine and its derivatives. VSM, vascular smooth muscle.

and inhibition of platelet aggregation (Fig. 2). Although bradycardia may not be the major factor in the onset of hypotensive action, it can probably contribute to the persistent hypotension in the later phase of berberine action. The antiproliferative effect on vascular smooth muscle may contribute to long-term beneficial effects of berberine on cardiovascular performance.

It is important, that research on the cardiovascular effects of berberine and structurally-related compounds, as well as berberine-containing plants, be continued, especially clinical investigations.

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