KB-R7943, a $\text{Na}^+/\text{Ca}^{2+}$ Exchange Inhibitor, Does Not Suppress Ischemia/Reperfusion Arrhythmias nor Digitalis Arrhythmias in Dogs

Shigeki Miyamoto, Bing-Mei Zhu, Kazunori Kamiya, Yoshinobu Nagasawa and Keitaro Hashimoto*

*Department of Pharmacology, University of Yamanashi, Faculty of Medicine,
Tamaho-cho, Nakakoma-gun, Yamanashi 409-3898, Japan*

Received April 12, 2002 Accepted July 29, 2002

ABSTRACT—KB-R7943 (2-[2-[4-(4-nitrobenzyloxy)phenyl]ethyl]isothiourea methanesulfonate) has been used as a pharmacological tool to block the Ca^{2+} influx-mode of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, which is thought to contribute to ischemia/reperfusion and digitalis arrhythmias. We examined effects of KB-R7943 on ischemia/reperfusion arrhythmias in beagle dogs anesthetized with sodium pentobarbital. Lead II ECG and BP were measured. KB-R7943 or the solvent (10% DMSO) was injected i.v. as a bolus, and 5 min later, the left anterior descending coronary artery was occluded for 30 min followed by reperfusion. KB-R7943 at 5 or 10 mg/kg increased BP without changing ECG parameters including the heart rate. Although 5 mg/kg KB-R7943 decreased the number of arrhythmic beats during the ischemic period, mortality due to ischemia/reperfusion was not decreased by KB-R7943 (5 and 10 mg/kg). KB-R7943 at 5 mg/kg also did not suppress the ouabain-induced arrhythmias. These negative results suggest that $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibition may not be a useful strategy of suppressing arrhythmias.

Keywords: KB-R7943, Ischemia/reperfusion, Digitalis, Arrhythmia, Dog

The $\text{Na}^+/\text{Ca}^{2+}$ exchanger is an essential component of regulators of intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) in many tissues. In the heart, Ca^{2+} extrusion from the cell is a major role played by the $\text{Na}^+/\text{Ca}^{2+}$ exchanger during normal action potential; however, the physiological role of Ca^{2+} influx via the exchanger is controversial (1–3). Under pathophysiological conditions such as digitalis toxicity and myocardial ischemia and reperfusion, intracellular Na^+ concentration is markedly increased (4, 5), favoring the reverse-mode of $\text{Na}^+/\text{Ca}^{2+}$ exchanger (6), Ca^{2+} influx-mode, leading to intracellular Ca^{2+} overload.

KB-R7943 (2-[2-[4-(4-nitrobenzyloxy)phenyl]ethyl]isothiourea methanesulfonate) is a first pharmacological tool to selectively suppress the reverse mode of $\text{Na}^+/\text{Ca}^{2+}$ exchanger, and many in vitro studies have shown antiarrhythmic effects of this compound (7–10). There are some in vivo studies evaluating antiarrhythmic effects of this compound on coronary ischemia/reperfusion models; and although on different models of cerebral ischemia/reperfusion models of rats, recently another new $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitor, SEA0400, was shown to attenuate cerebral reperfusion injury in vivo in rats (11). As for ischemia

/reperfusion arrhythmias, the results of $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitors on in vivo arrhythmias are still controversial. In rats, Nakamura et al. (12) showed that the KB-R7943 suppressed ischemia/reperfusion arrhythmias, whereas Lu et al. (13) did not observe such antiarrhythmic effects, partly due to the different method of drug administration used in these reports. It has been reported that KB-R7943 has additional effects to inhibit the Ca^{2+} , Na^+ and K^+ channels (14, 15), and recently Kimura et al. (16) showed that KB-R7943 even inhibits the forward-mode (Ca^{2+} extrusion mode) of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger with similar IC_{50} to inhibit the reverse-mode. Since there have been few reports clarifying antiarrhythmic effects of KB-R7943 on large animal ischemia/reperfusion arrhythmias in vivo where Ca^{2+} overload is the important mechanism of generation, we examined KB-R7943 on canine ischemia/reperfusion induced and digitalis induced arrhythmias, which are more relevant to predict clinical efficacy of antiarrhythmic drugs and on which there have no reports examining $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitors.

MATERIALS AND METHODS

These animal experiments were approved by the Yamanashi Medical University Animal Experimentation Com-

*Corresponding author. FAX: +81-55-273-6739
E-mail: keitaroh@res.yamanashi-med.ac.jp

mittee, and animals were obtained through the Animal Laboratory for Research of Yamanashi Medical University.

Coronary ligation and reperfusion arrhythmias

Twenty-eight adult beagle dogs of either sex, weighing 9.0–11.5 kg, were intravenously anesthetized with 30 mg/kg pentobarbital sodium. After tracheal intubation (20 ml/kg, 15 strokes/min, SN-480-4; Shinano, Tokyo), anesthesia was maintained by intravenous infusion of pentobarbital sodium (5 mg/kg per hour). As reported earlier (17), the chest was opened, and the left anterior descending coronary artery was isolated just proximal to the first diagonal branch of the left anterior descending coronary artery. The left anterior descending coronary artery was ligated using a silk thread for 30 min, and then the ligation was released to observe reperfusion responses. Because the incidence of reperfusion-arrhythmias is known to be quite variable, experiments were randomized by coin-flip in paired dogs; one received KB-R7943 (intravenous bolus injection 5 min before coronary ligation), and the other received 10% dimethyl sulfoxide (DMSO), the solvent of KB-R7943. Each dog received a drug or solvent injection once.

Bipolar electrodes were sutured on the border zone of the ischemic area of the left ventricle for continuous recording of the ventricular electrogram. The lead II electrocardiogram (ECG) and arterial blood pressure through a cannula in the femoral artery were also continuously monitored. The QT interval was assessed from the lead II electrocardiogram, and the ventricular surface electrogram was measured from the onset of the QRS complex to the end of the T-wave in the lead II ECG. The corrected QT interval (QTc) was calculated using Bazett's formula, $QTc = QT / \sqrt{RR}$. The corrected JT interval (JTc) was calculated by the formula, $JTc = JT / \sqrt{RR}$, in which the JT interval was calculated by subtracting the QRS duration from the QT interval. The ECG, ventricular surface electrogram and blood pressure were recorded with a polygraph system (Nihon Kohden, Tokyo). The femoral vein was also cannulated for administration of KB-R7943 (2–10 mg/kg) or the solvent (10% DMSO).

Ouabain-induced arrhythmia

Six adult beagle dogs of either sex, weighing 8.0–11 kg, were intravenously anesthetized with 30 mg/kg pentobarbital sodium followed by intravenous infusion of pentobarbital sodium (5 mg/kg per hour). As reported earlier (18), 40 μ g/kg ouabain was injected intravenously and then followed by an additional 10 μ g/kg every 20 min until stable ventricular tachycardia was produced, usually at cumulative dose of 60 to 70 μ g/kg. In the absence of drug administration, the resulting arrhythmias remained stable for more than 60 min, as reported by us (17). KB-R7943

was administered as an intravenous bolus injection at a dose of 5 mg/kg. The lead II ECG, atrial electrogram from catheter tip electrodes in the right atrium, and the instantaneous and mean blood pressure were continuously recorded.

The severity of ouabain-induced arrhythmia was evaluated by the arrhythmic ratio, which was calculated by dividing the number of premature ventricular ectopic beats (PVC) by the number of the total heart rate, i.e., the number of ventricular ectopic beats plus the number of conducted beats; and the ventricular beats were judged by the different shape of the ventricular complex from the normal QRS complex. The arrhythmic ratio before drug infusion was almost 1, as shown in the control values of Fig. 4, and there was no spontaneous improvement in this ratio as previously reported by us (17).

Drugs

The drug used in this study was KB-R7943, which was kindly provided by Nippon Organon (Tokyo). Dimethyl sulfoxide (DMSO) (Wako, Osaka), pentobarbital sodium (Tokyo Kasei Kogyo, Tokyo) and ouabain octahydrate (Aldrich, Milwaukee, WI, USA) were purchased.

Statistical analyses

Analysis of variance (ANOVA) followed by Dunnett's multiple comparison test was performed to evaluate drug-induced changes in the blood pressure, heart rate and ECG parameters. Differences in the incidence of arrhythmias between KB-R7943 groups and 10% DMSO group were analyzed with Fisher's exact probability test. All data are expressed as the mean $\pm$ S.E.M. Differences were regarded as significant if the *P* values were less than 0.05.

RESULTS

Effects of KB-R7943 on hemodynamic- and ECG parameters

Figure 1 shows effects of 5 and 10 mg/kg (*n* = 8 and 6, respectively) KB-R7943 on the blood pressure, heart rate and ECG parameters. At 5 min after KB-R7943 infusion, the systolic blood pressure was significantly increased by 10 mg/kg, but not by 5 mg/kg and the diastolic level was significantly increased by both doses of KB-R7943. Mean blood pressure was also increased by 5 and 10 mg/kg KB-R7943. Ten percent DMSO, the solvent, did not change the systolic, diastolic and mean blood pressure (data not shown). KB-R7943 at 5 and 10 mg/kg did not change the PQ interval, QRS duration, QTc and JTc intervals. Occasionally, the heart rate was slightly decreased by KB-R7943 as shown in Fig. 1A, although the solvent of KB-R7943 (10% DMSO) also tended to show a similar change.

Fig. 1. Effects of KB-R7943 on the blood pressure, heart rate and ECG parameters. A: Representative trace of blood pressure, mean blood pressure and heart rate. B and C: Summarized results of effects of 5 and 10 mg/kg KB-R7943, respectively. ** $P < 0.01$ vs before drug values. MBP: mean blood pressure, BP: blood pressure, HR: heart rate, sys: systolic blood pressure, dia: diastolic blood pressure.

Effects of KB-R7943 on ischemia/reperfusion arrhythmias

Figures 2 and 3 show the summary of the effects of 5 and 10 mg/kg KB-R7943 on the coronary ligation-reperfusion arrhythmias, respectively. At 5 mg/kg, KB-R7943 tended to decrease the arrhythmia during the 30-min ischemia, as shown in the increase of the blank bar (normal

sinus rhythm) in Fig. 2, and the mean number of arrhythmic beats including all the PVC and ventricular tachycardia (VT) decreased from the control group, 338 ± 123 beats/30 min ($n = 8$) to 133 ± 59 beats/30 min after injection of KB-R7943 (statistically not significant); however, if we used the combined control group data of 5 mg/kg and

10% DMSO

KBR-7943, 5 mg/kg

Fig. 2. Effects of 5 mg/kg KB-R7943 on ischemia/reperfusion arrhythmias in dogs. Each column indicates the responses of each dog. Normal: sinus rhythm, PVC: premature ventricular contractions, VT: ventricular tachycardia, VF: ventricular fibrillation.

10 mg/kg, the mean number of arrhythmic beats was 433 ± 92 beats/30 min ($n = 14$), so that the decrease was statistically significant ($P = 0.03$). Neither a higher concentration of 10 mg/kg ($n = 6$) nor a lower one of 2 mg/kg ($n = 6$) showed such an antiarrhythmic effect. In the 5 mg/kg KB-R7943 treated group, 4 dogs out of 8 died of ventricular fibrillation (VF) by the ischemia/reperfusion procedure, while in the control group, 6 dogs out of 8 died. The decrease in the mortality in KB-R7943 treated dogs was not significant as compared to the control dogs. As shown in Fig. 3, 4 dogs out of 6 died in the control group, while 5 dogs out of 6 died in the 10 mg KB-R7943 treated group after the ischemia/reperfusion procedure, indicating that mortality was not improved by a higher dose of 10 mg/kg KB-R7943. At 10 mg/kg, KB-R7943 did not decrease the number of arrhythmic beats including the PVC and VT

and numbers of PVC during ischemia.

Effects of KB-R7943 on ouabain-induced arrhythmias

Figure 4 shows that 5 mg/kg KB-R7943 did not suppress the ouabain-induced arrhythmia, although there was a tendency for arrhythmic beats to decrease after the KB-R7943 injection. KB-R7943 tended to increase the blood pressure soon after injection, but later the blood pressure tended to decrease, probably reflecting the decrease of the concentration of ouabain without supplementation after establishment of digitalis-induced arrhythmias as shown in our previous report (17). The decrease of the arrhythmic ratio in the upper panel of the figure may also reflect the decrease of the arrhythmogenic effect of ouabain in the later part of the experiment as shown in our previous report (17).

10% DMSO

KBR-7943, 10 mg/kg

Fig. 3. Effects of 10 mg/kg KB-R7943 on ischemia/reperfusion arrhythmias in dogs. Each column indicates the responses of each dog.

DISCUSSION

In this study, 5 and 10 mg/kg KB-R7943 did not decrease the mortality due to VF during the 30-min ischemia and reperfusion in dogs. The only cardioprotective effect observed in this study was a decrease of the mean number of arrhythmic beats during ischemia ($P = 0.03$) after administration of 5 mg/kg KB-R7943. A lower concentration of 2 mg/kg KB-R7943 also did not suppress the mortality after the ischemia/reperfusion (results not shown, 4 out of 6 dogs died). In rats, Nakamura et al. (12) showed that 10 mg/kg, but not 1 mg/kg, KB-R7943 suppressed ischemia/reperfusion arrhythmias, whereas Lu et al. (13) did not observe such antiarrhythmic effects by 5 mg/kg KB-R7943 on ischemia/reperfusion arrhythmia. Our results support the latter observation and suggest that KB-R7943 does not suppress *in vivo* ischemia/reperfusion arrhythmias in dogs, although other types of cardioprotection of this compound have been demonstrated in *in vitro* studies (7, 8). In addition, no apparent antiarrhythmic effects of KB-R7943 on canine ouabain-induced arrhythmia were

observed (Fig. 4). Watano et al. (19) have reported that pretreatment with 3 mg/kg KB-R7943 delays the time necessary for the appearance of arrhythmias and cardiac arrest after ouabain infusion in the guinea pig. One of the reasons for this discrepancy might be due to the different protocols. In this study, KB-R7943 was applied after digitalis arrhythmia was fully elicited by ouabain, whereas Watano et al. (19) applied KB-R7943 before starting the ouabain infusion. Our previous reports showed that class I antiarrhythmic drugs are effective in ouabain-induced arrhythmias (20, 21), and it is widely accepted that the ouabain-induced arrhythmias are due to the increase in intracellular Na^+ concentrations ($[\text{Na}^+]_i$) followed by intracellular Ca^{2+} concentration. It is widely accepted that both myocardial ischemia and digitalis induce a rapid and large increase in $[\text{Na}^+]_i$ and then induce fatal arrhythmias including ventricular fibrillation (5). Therefore, our results suggest that KB-R7943, at least *in vivo*, has no inhibitory effect on arrhythmias caused probably by $[\text{Na}^+]_i$ overload with subsequent Ca^{2+} overload. Noble and his coworkers (22) suggest that the inhibition of $\text{Na}^+/\text{Ca}^{2+}$ exchanger is

Fig. 4. Effects of 5 mg/kg KB-R7943 on ouabain-induced arrhythmia (upper panel) and blood pressure (lower panel). After about 60–70 $\mu\text{g/kg}$ ouabain, the mean blood pressure (mBP) at 0 time (after KB-R7943 administration) is higher than that in the normal anesthetized animal, such as those shown in Fig. 1. Values are means $\pm$ S.E.M.

arrhythmogenic, but the activation of the exchanger is anti-arrhythmic during ischemia/reperfusion in their simulation based on the OXSOFT models. Although KB-R7943 is the only relatively selective $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitor available, it is now shown to also inhibit K^+ , Ca^{2+} and Na^+ channels with IC_{50} value 7, 8 and 14 μM (14). In addition, recent papers (15, 16) showed that KB-R7943 inhibits not only the reverse-mode, but also the forward-mode of $\text{Na}^+/\text{Ca}^{2+}$ exchanger with similar IC_{50} (about 1 μM), indicating direction-independent block. These multiple, and thus not selective, inhibitory effects of this compound make the explanation of disability of inhibiting ischemia/reperfusion- and ouabain-induced arrhythmias in this study difficult. However, it is also known that the role of $\text{Na}^+/\text{Ca}^{2+}$ exchangers in physiological regulation of intracellular Ca^{2+} concentration in the heart and vascular systems are not the same in different animals, especially between guinea pigs and rats, and at various pathophysiological conditions (23–27). Unfortunately, there have been no report com-

paring $\text{Na}^+/\text{Ca}^{2+}$ exchanger activities in canine tissues compared to another animal. Another possibility is that plasma concentrations of KB-R7943 are too low to inhibit the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, and a higher dose of KB-R7943 might be expected to suppress the $[\text{Na}^+]_i$ overload-induced arrhythmias. However, 10 mg/kg used in this study must be near the maximum volume possible to be applied to whole animals without effects of its solvent on hemodynamics. Lower concentrations of KB-R7943 might be too low to suppress ischemia/reperfusion arrhythmias, because it has been reported that 1 mg/kg KB-R7943 did not suppress the ischemia/reperfusion arrhythmias in a report showing the antiarrhythmic effect of KB-R7943 during ischemia/reperfusion in vivo (12).

Many in vitro studies have suggested that KB-R7943 elicits negative inotropic effects by inhibiting various ion channels (28–30). In this study, however, KB-R7943 increased the blood pressure without significant change in the electrocardiographic parameters (Fig. 1), although this effect was not observed in the presence of ouabain (Fig. 4). Recently, it has been reported that not only Ni^{2+} , a non-selective blocker of $\text{Na}^+/\text{Ca}^{2+}$ exchanger, but also KB-R7943 increases vascular resistance in rats (31). The vasoconstrictive effect of this compound may contribute to the increase in the blood pressure observed in this study, but one should also bear in mind the species difference in the role of $\text{Na}^+/\text{Ca}^{2+}$ exchangers.

In summary, our results suggest that KB-R7943 has no protective effect on ischemia/reperfusion and ouabain-arrhythmias in dogs.

REFERENCES

- 1 Leblanc N and Hume JR: Sodium current-induced release of calcium from cardiac sarcoplasmic reticulum. *Science* **248**, 372–376 (1990)
- 2 Sham JSK, Cleemann L and Morad M: Gating of the cardiac Ca^{2+} release channel: the role of Na^+ current and $\text{Na}^+/\text{Ca}^{2+}$ exchange. *Science* **255**, 850–853 (1992)
- 3 Philipson KD and Nicoll DA: Sodium-calcium exchange: a molecular perspective. *Annu Rev Physiol* **62**, 111–133 (2000)
- 4 Pike MM, Kitakaze M and Marban E: ^{23}Na -NMR measurements of intracellular sodium in intact perfused ferret hearts during ischemia and reperfusion. *Am J Physiol (Heart Circ Physiol)* **259**, H1767–H1773 (1990)
- 5 Imahashi K, Kusuoka H, Hashimoto K, Yoshioka J, Yamaguchi H and Nishimura T: Intracellular sodium accumulation during ischemia as the substrate for reperfusion injury. *Circ Res* **84**, 1401–1406 (1999)
- 6 Noble D, LeGuennec JY and Winslow R: Functional roles of sodium-calcium exchange in normal and abnormal cardiac rhythm. *Ann NY Acad Sci* **779**, 480–488 (1996)
- 7 Ladilov Y, Haffner S, Balser-Schafer C, Maxeiner H and Piper HM: Cardioprotective effects of KB-R7943: a novel inhibitor of the reverse mode of $\text{Na}^+/\text{Ca}^{2+}$ exchanger. *Am J Physiol (Heart Circ Physiol)* **276**, H1868–H1876 (1999)

- 8 Mukai M, Terada H, Sugiyama S, Satoh H and Hayashi H: Effects of a selective inhibitor of $\text{Na}^+/\text{Ca}^{2+}$ exchange, KB-R7943, on reoxygenation-induced injuries in guinea pig papillary muscles. *J Cardiovasc Pharmacol* **35**, 121–128 (2000)
- 9 Satoh H, Ginsburg KS, Qing K, Terada H, Hayashi H and Bers DM: KB-R7943 block of Ca^{2+} influx via $\text{Na}^+/\text{Ca}^{2+}$ exchange does not alter twitches or glycoside inotropy but prevents Ca^{2+} overload in rat ventricular myocytes. *Circulation* **101**, 1441–1446 (2000)
- 10 Elias CL, Lukas A, Shurraw S, Scott J, Omelchenko A, Gross GJ, Hnatowich M and Hryshko LV: Inhibition of $\text{Na}^+ \cdot \text{Ca}^{2+}$ exchange by KB-R7943: transport mode selectivity and antiarrhythmic consequences. *Am J Physiol (Heart Circ Physiol)* **281**, H1334–H1345 (2001)
- 11 Matsuda T, Arakawa N, Takuma K, Kishida Y, Kawasaki Y, Sakaue M, Takahashi K, Takahashi T, Suzuki T, Ota T, Hamano-Takahashi A, Onishi M, Tanaka Y, Kameo K and Baba A: SEA0400, a novel and selective inhibitor of the $\text{Na}^+ \cdot \text{Ca}^{2+}$ exchanger, attenuates reperfusion injury in the in vitro and in vivo cerebral ischemic models. *J Pharmacol Exp Ther* **298**, 249–256 (2001)
- 12 Nakamura A, Harada K, Sugimoto H, Nakajima F and Nishimura N: Effects of KB-R7943, a novel $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitor, on myocardial ischemia/reperfusion injury. *Folia Pharmacol Jpn (Nippon Yakurigaku Zasshi)* **111**, 105–115 (1998) (text in Japanese with English abstract)
- 13 Lu HR, Yang P, Remeysen P, Saels A, Dai DZ and De Clerck F: Ischemia/reperfusion-induced arrhythmias in anaesthetized rats: a role of Na^+ and Ca^{2+} influx. *Eur J Pharmacol* **365**, 233–239 (1999)
- 14 Watano T, Kimura J, Morita T and Nakanishi H: A novel antagonist, No. 7943, of the $\text{Na}^+/\text{Ca}^{2+}$ exchange current in guinea-pig cardiac ventricular cells. *Br J Pharmacol* **119**, 555–563 (1996)
- 15 Tanaka H, Nishimaru K, Aikawa T, Hirayama W, Tanaka Y and Shigenobu K: Effect of SEA0400, a novel inhibitor of sodium-calcium exchanger, on myocardial ionic currents. *Br J Pharmacol* **135**, 1096–1100 (2002)
- 16 Kimura J, Watano T, Kawahara M, Sakai E and Yatabe J: Direction-independent block of bi-directional $\text{Na}^+/\text{Ca}^{2+}$ exchange current by KB-R7943 in guinea-pig cardiac myocytes. *Br J Pharmacol* **128**, 969–974 (1999)
- 17 Awaji T, Wu ZJ and Hashimoto K: Acute antiarrhythmic effects of intravenously administered amiodarone on canine ventricular arrhythmia. *J Cardiovasc Pharmacol* **26**, 869–878 (1995)
- 18 Hashimoto K, Ishii M, Komori S and Mitsuhashi H: Canine digitalis arrhythmia as a model for detecting Na-channel blocking antiarrhythmic drugs: a comparative study using other canine arrhythmia models and the new antiarrhythmic drugs, propafenone, tocainide, and SUN 1165. *Heart Vessels* **1**, 29–35 (1985)
- 19 Watano T, Harada Y, Harada K and Nishimura N: Effect of $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitor, KB-R7943 on ouabain-induced arrhythmias in guinea-pigs. *Br J Pharmacol* **127**, 1846–1850 (1999)
- 20 Hashimoto K, Haruno A, Matsuzaki T, Sugiyama A and Akiyama K: Effects of antiarrhythmic drugs on canine ventricular arrhythmia models: which electrophysiological characteristics of drugs are related to their effectiveness? *Cardiovasc Drugs Ther* **5**, 805–817 (1991)
- 21 Xue YX, Arita J, Aye NN and Hashimoto K: Effects of an antiarrhythmic drug A-2545 on canine ventricular arrhythmia models; comparison with mexiletine and flecainide. *Naunyn Schmiedebergs Arch Pharmacol* **358**, 649–656 (1998)
- 22 Ch'en FF, Vaughan-Jones RD, Clarke K and Noble D: Modeling myocardial ischaemia and reperfusion. *Prog Biophys Mol Biol* **69**, 515–538 (1998)
- 23 Bers DM, Bassani JW and Bassani RA: Na-Ca exchange and Ca fluxes during contraction and relaxation in mammalian ventricular muscle. *Ann NY Acad Sci* **779**, 430–442 (1996)
- 24 Menick DR, Barnes KV, Thacker UF, Dawson MM, McDermott DE, Rozich JD, Kent RL and Cooper G IV: The exchange and cardiac hypertrophy. *Ann NY Acad Sci* **779**, 489–501 (1996)
- 25 Litwin SE and Bridge JHB: Enhanced $\text{Na}^+ \cdot \text{Ca}^{2+}$ exchange in the infarcted heart; implications for excitation-contraction coupling. *Circ Res* **81**, 1083–1093 (1997)
- 26 Bersohn MM, Philipson KD and Fukushima JY: Sodium-calcium exchange and sarcolemmal enzymes in ischemic rabbit hearts. *Am J Physiol (Cell Physiol)* **242**, C288–C295 (1982)
- 27 Shigekawa M and Iwamoto T: Cardiac $\text{Na}^+ \cdot \text{Ca}^{2+}$ exchange; molecular and pharmacological aspects. *Circ Res* **88**, 864–876 (2001)
- 28 Fujita S and Endoh M: Influence of a $\text{Na}^+ \cdot \text{H}^+$ exchange inhibitor ethylisopropylamiloride, a $\text{Na}^+ \cdot \text{Ca}^{2+}$ exchange inhibitor KB-R7943 and their combination on the increases in contractility and Ca^{2+} transient induced by angiotensin II in isolated adult rabbit ventricular myocytes. *Naunyn Schmiedebergs Arch Pharmacol* **360**, 575–584 (1999)
- 29 Yang HT, Sakurai K, Sugawara H, Watanabe T, Norota I and Endoh M: Role of $\text{Na}^+/\text{Ca}^{2+}$ exchange in endothelin-1-induced increases in Ca^{2+} transient and contractility in rabbit ventricular myocytes: pharmacological analysis with KB-R7943. *Br J Pharmacol* **126**, 1785–1795 (1999)
- 30 Kurogouchi F, Furukawa Y, Zhao D, Hirose M, Nakajima K, Tsuboi M and Chiba S: A $\text{Na}^+/\text{Ca}^{2+}$ exchanger inhibitor, KB-R7943, caused negative inotropic responses and negative followed by positive chronotropic responses in isolated, blood-perfused dog heart preparations. *Jpn J Pharmacol* **82**, 155–163 (2000)
- 31 Schweda F, Seebauer H, Kramer BK and Kurtz A: Functional role of sodium-calcium exchange in the regulation of renal vascular resistance. *Am J Physiol (Renal Physiol)* **280**, F155–F161 (2001)