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Antiarrhythmic Effects of KR-32570, a Novel Na^+-H^+ Exchanger Inhibitor, on Ischemia/Reperfusion-Induced Arrhythmias

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Abstract – The present study was performed to evaluate antiarrhythmic effects of KR-32570, a novel inhibitor of sodium hydrogen exchanger subtype-1 (NHE-1), in rat arrhythmia induced by focal ischemia and reperfusion. During ischemia, KR-32570 significantly decreased the number of premature ventricular contraction (PVC) from 152.0 times to 75.5, 52.4 and 20.0 times for 0.1, 0.3 and 1.0 mg/kg, respectively ($p<0.05$) and the duration of ventricular tachycardia (VT) from 88.1 s to 35.8, 7.7 and 1.3 s, respectively ($p<0.05$) in anesthetized rats subjected to 10-min coronary occlusion and 10-min reperfusion. The duration of ventricular fibrillation (VF) was completely inhibited by the treatment of KR32570 at all doses tested. KR-32570 significantly delayed onset time of PVC and VT occurring after occlusion of coronary artery. Similarly to ischemia-induced arrhythmia, KR-32570 significantly decreased reperfusion-induced arrhythmia including PVC (41.3, 21.5, 11.3 and 6.6 times at vehicle, 0.1, 0.3 and 1.0 mg/kg, respectively, $p<0.05$) and VT (100.5, 64.2, 25.8 and 25.2 s, respectively, $p<0.05$), and VF (86.9, 27.5, 6.9 and 0 s, respectively, $p<0.05$). Moreover, KR-32570 dose-dependently decreased the incidence of mortality occurring after reperfusion (41, 27, 18 and 0% at vehicle, 0.1, 0.3, 1.0 mg/kg, respectively). These results suggest that KR-32570 has a potent antiarrhythmic effect in rat arrhythmia induced by ischemia and reperfusion.

Key words □ antiarrhythmic effect, sodium hydrogen exchanger, KR-32570

Sudden cardiac death is a leading public health problem today and has been most frequently caused by malignant ventricular tachyarrhythmias related to the short- and long-term actions of ischemic heart disease (Hinkle and Thaler, 1982; Bayes et al., 1989). Such lethal arrhythmias have usually occurred during ischemia and reperfusion (Pogwizd and Corr, 1987). Recently, many experimental evidences indicate that Na^+/H^+ exchanger subtype-1 (NHE-1) is involved in myocardial ischemia/reperfusion-induced arrhythmia (Scholz and Albus, 1995; Gumina *et al.*, 2000; Karmazyn, 2002). With myocardial ischemia, anaerobic metabolism and hydrolysis of ATP raise an accumulation of intracellular protons (Dennis *et al.*, 1991) which activates the NHE-1 leading to an increase in intracellular sodium concentration. This leads to intracellular Ca^{2+} overload through the Na^+-Ca^{2+} exchange system in the ischemic myocardium (Frelin *et al.*, 1984; Tani and Neely, 1990; Litwin and Bridge, 1997). During reperfusion, extracellular H^+ rapidly decreases increasing the intracellular to extracellular H^+ gradient. This large H^+ gradient activates NHE-1, which enhances intracellular Na^+ and lead, through the Na^+/Ca^{2+} exchanger, to accumulation of Ca^{2+} during reperfusion (Tani and Neely, 1989; Stromer *et al.*, 2000). Finally, an abnormal intracellular accumulation of Ca^{2+} during ischemia and reperfusion contributes to myocardial cell death, arrhythmias and stunning (Thandroyen *et al.*, 1991; DuToit and Opie, 1993; Pogwizd, 2001).

Inhibition of the NHE-1 during ischemia and reperfusion produces substantial cardioprotective effect by blocking the damage caused by the coupled exchanger mechanism (Scholz and Albus, 1995; Karmazyn, 1996). A number of NHE-1 inhibitor also has been reported to reduce both ischemia/reperfusion-induced arrhythmias (Aye *et al.*, 1997; Gumina *et al.*, 2000; Zhu *et al.*, 2002). Recently, in our efforts to discover novel inhibitors of NHE-1, we have found that a series of analogues of (5-phenylfuran-2-carbonyl)guanidine exhibited potent inhibitory effects on NHE-1. Especially [5-(2-Methoxy-5-chloro-5-phenyl)furan-2-ylcarbonyl]guanidine (KR-32570) showed a great potency on NHE-1 activity and a significantly improved cardiac contractile function (Lee *et al.*, 2005), and a tremendous reduction in the myocardial infarction in rats and dogs

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(unpublished data). The aim of the present study was to evaluate antiarrhythmic effects of KR-32570 in rat arrhythmia model induced by ischemia/reperfusion.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley (S. D.) rats (380-420g) were purchased from Orient Co. (Seoul, Korea). The animals were conditioned for 1 week at 22.5±1°C with a constant humidity of 55±5%, a cycle of 12-h light/dark, and free access to food and tap water.

Materials

KR-32570 was synthesized at organic synthesis division of Korea Research Institute of Chemical Technology (Daejon, Korea), and dissolved in 50% polyethyleneglycol 400 in saline for intravenous administration. Sodium pentobarbital was purchased from Hanlim Pharmaceutical Co. (Seoul, Korea). All drugs and reagents were prepared just prior to use.

Antiarrhythmic effects in rat model of ischemic heart

S. D. rats were anesthetized with sodium pentobarbital (35 mg/kg, i.v.) as previously described (Lee *et al.*, 2001; 2004). The trachea was intubated and connected to a rodent ventilator (SAR 830/P ventilator, CWE Inc., Ardmore, PA, USA) for artificial ventilation with room air (stroke volume, 10 ml/kg; 60 strokes/min). The femoral artery and vein were catheterized for measurement of blood pressure and for drug administration, respectively. Arterial blood pressure was continuously monitored via an Isotec pressure transducer (Hugo Sachs Electronic) connected to a physiograph (WR 3300 Linearcorder, Graphtec, Tokyo, Japan). Electrocardiogram and heart rate (HR) were measured by Lead II using an electrocardiogram/rate coupler (Type 576; Hugo Sachs Electronic), both parameters being analyzed by the computer program (PONEMAH physiology platform - model P3 Plus, Gould Inc., Cleveland, OH, USA). Body temperature was maintained at 37°C with a homeothermic blanket control unit. The chest was opened by a left thoracotomy in the fifth to sixth intercostal space and the pericardium was incised. The heart was gently exteriorized by pressure on the chest, and a ligature (5-0 silk) was placed around the left anterior descending coronary artery. The heart was quickly repositioned in the thoracic cavity with the ligature ends exteriorized. Both ends of the ligature were passed through a polyethylene tube (PE100, 1.5 cm long) and the rats were allowed to stabilize for 10 min. During an equilibration period rats with spontaneous arrhythmias or a mean arterial pressure below 70 mmHg or both were not used.

For the coronary artery occlusion, PE 100 was pressed on the surface of the heart directly above the coronary artery and a small hemostat was applied to clamp the tube for 10 min. Reperfusion was allowed for 10 min by unclamping the tube and the ligature. KR-32570 was intravenously administered by bolus injection at 5 min prior to ischemia (1 ml/kg). Definitions of arrhythmias were based on the description of the Lambeth Conventions (Walker *et al.*, 1988). Ectopic ventricular activity was categorized as a single premature ventricular contraction (PVC), ventricular tachycardia (VT, 4 or more consecutive PVC) or ventricular fibrillation (VF, inability to distinguish individual QRS complexes and to measure the rate). Reference was made to the blood pressure tracings to confirm which type of ectopic activity was occurring, particularly to distinguish between the polymorphic VT and VF. When the former occurred, the blood pressure was usually still pulsatile, whereas with VF the blood pressure fell rapidly towards zero and was no longer pulsatile. VF may be sustained or may revert spontaneously to a normal sinus rhythm in the rat (Curtis and Hearse, 1989).

Statistical analysis

All values are expressed as mean±S.E.M. Data were analyzed by paired Student's *t*-test and one-way analysis of variance (ANOVA) followed by the Dunnett's test for multiple comparisons (Sigma Stat, Jandel Co., San Rafael, CA, U.S.A.). In all comparisons, the difference was considered to be statistically significant at $p<0.05$.

RESULTS

Antiarrhythmic effects in rat model of ischemic heart

In vehicle-treated group, an anesthetized rat that underwent 10-min coronary occlusion followed by 10-min reperfusion caused severe arrhythmias (Table I). The duration of VF during reperfusion was about 2.5 times longer than that of during ischemia (86.9±18.7 s and 34.8±12.6 s, respectively), although an increase of the number of PVC during reperfusion was smaller than that of during ischemia (41.3±11.3 and 152.0± 20.5, respectively), which suggest that a 10-min ischemia/10-min reperfusion in rats caused arrhythmias more severely during reperfusion than that of during ischemia.

In ischemia-induced arrhythmia, KR-32570 significantly

Table I. The number of PVC and the duration of VT and VF in vehicle-treated rats subjected to 10 min occlusion of left anterior descending coronary artery followed by 10 min reperfusion.

	During ischemia	During reperfusion
Number of PVC (times)	152.0±20.5	41.3±11.3*
Duration of VT (s)	88.1±14.9	100.5±24.7
Duration of VF (s)	34.8±12.6	86.9±18.7*
Onset time of PVC (min)	4.7±0.8	
Onset time of VT (min)	4.8±0.5	
Onset time of VF (min)	6.4±0.3	

PVC, premature ventricular contraction; VT, ventricular tachycardia; VF, ventricular fibrillation. *P<0.05, significantly different from the values during ischemia (n=10).

and dose-dependently decreased the number of PVC (75.5± 18.5, 52.4±15.4 and 20.0±10.4 times at 0.1, 0.3 and 1.0 mg/kg, respectively, p<0.05) compared with vehicle-treated group (152.0±20.5 times, Fig. 1A). KR-32570 significantly decreased the duration of VT also (35.8±8.4, 7.7±5.3 and 1.3±0.7 s at 0.1, 0.3 and 1.0 mg/kg, respectively, p<0.05) compared with vehicle-treated group (88.1±14.9 s, Fig 1B). The duration of VF was completely inhibited by the treatment of KR-32570 at all doses tested (Fig. 1C). In vehicle-treated group, PVC commenced between 1-6min after coronary occlusion (4.7±0.8 min). This onset time of PVC was delayed by the treatment of KR-32570 (6.1±0.5, 5.6±0.9 and 6.9±0.6 min at 0.1, 0.3 and 1.0 mg/kg, respectively, p<0.05). KR-32570 significantly delayed onset time of VT occurring after occlusion of coronary artery (7.4±0.4, 7.3±0.7 and 8.9±0.6 min at 0.1, 0.3 and 1.0 mg/kg, respectively, p<0.05) compared with vehicle-treated group (4.8±0.5 min).

In reperfusion-induced arrhythmia, KR-32570 also showed a similar pattern and potency with that of ischemia-induced arrhythmia. KR-32570 dose-dependently decreased the number of reperfusion-induced PVC (41.3±11.3, 21.5±5.3, 11.3± 3.4 and 6.6±1.5 times at vehicle, 0.1, 0.3 and 30 mg/kg, respectively, p<0.05, Fig 2A), the duration of VT (100.5± 24.7, 64.2 ± 11.1, 25.8±8.2 and 25.2±5.7 s, respectively, p<0.05, Fig 2B) and the duration of VF (86.9±18.6, 27.5±10.9, 6.9±2.9 and 0± 0 s, respectively, p<0.05, Fig. 2C). During reperfusion, PVC, VT and VF developed immediately after reperfusion (within 30 s) in all groups, without significant differences.

In vehicle-treated group, a number of rats subjected ischemia/ reperfusion was dead within 2 min after reperfusion (7 of 17 rats, 41.2%, Fig. 3). However, the incidence of reperfusion-induced mortality significantly reduced by KR32570 in a dose-dependent manner (4 of 15 rats, 26.7%; 2 of 11 rats, 18.2%; 0 of 7 rats, 0% at 0.1, 0.3, 30 mg/kg, respectively).

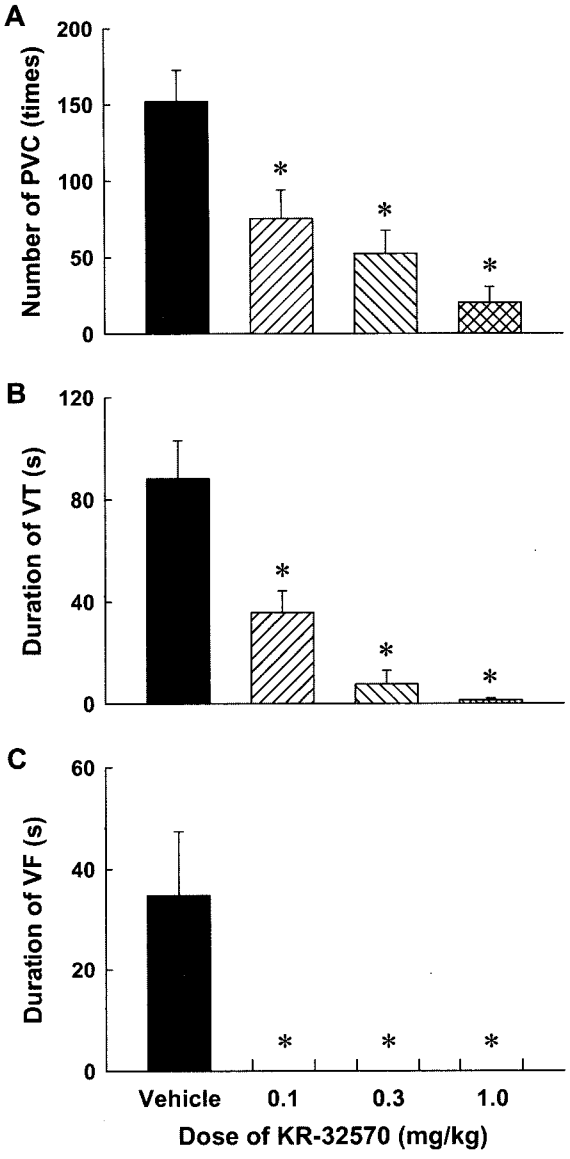

Fig. 1. Effects of KR-32570 on ischemia-induced premature ventricular contraction (PVC), ventricular tachycardia (VT) and ventricular fibrillation (VF) in rats subjected to 10 min occlusion of left anterior descending coronary artery followed by 10 min reperfusion. Vehicle (n=10), KR-32570: 0.1 (n=11), 0.3 (n=9) and 1.0 (n=7) mg/kg. *P<0.05, significantly different from the vehicle-treated group.

Hemodynamic parameters in rat model of ischemic heart

The effect of KR-32570 on mean arterial pressure (MAP) and HR was examined before and at 5 min after administration of the compounds, at 5 and 10 min after ischemia, and at 5 and 10 min after reperfusion (Table II). In vehicle-treated group, MAP of the rats slightly increased after administration of 50 % polyethyleneglycol 400 (1 ml/kg). KR-32570 did not cause any significant changes in MAP and HR compared with the vehi-

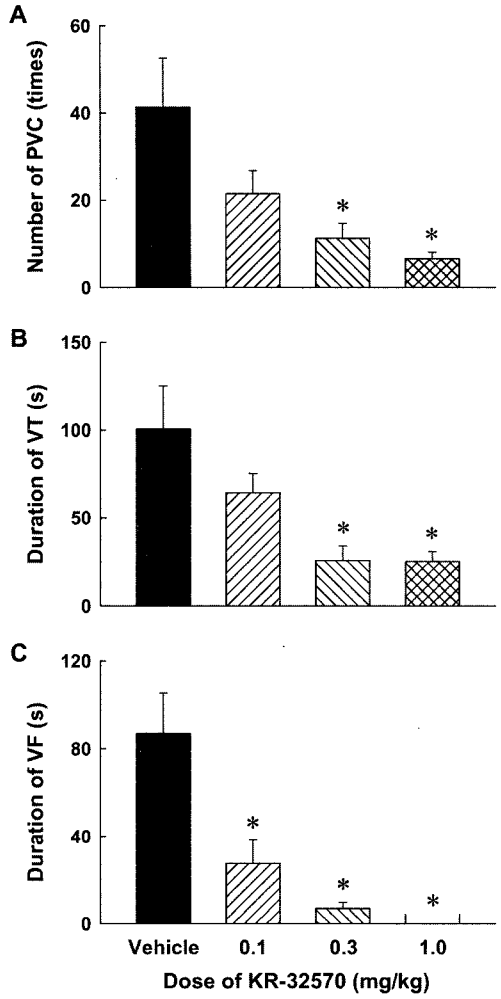

Fig. 2. Effects of KR-32570 on reperfusion-induced premature ventricular contraction (PVC), ventricular tachycardia (VT) and ventricular fibrillation (VF) in rats subjected to 10 min occlusion of left anterior descending coronary artery followed by 10 min reperfusion. Vehicle (n=10), KR-32570: 0.1 (n=11), 0.3 (n=9) and 1.0 (n=7) mg/kg. *P<0.05, significantly different from the vehicle-treated group (n=10).

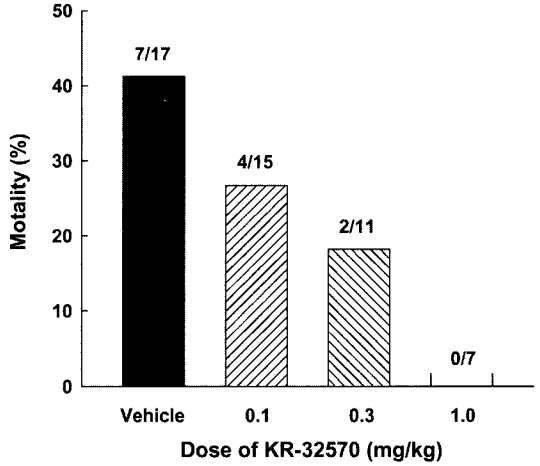

Fig. 3. Dose-dependent prevention of reperfusion-induced mortality in rats subjected to 10 min occlusion of left anterior descending coronary artery followed by 10 min reperfusion. Vehicle (n=10), KR-32570: 0.1 (n=11), 0.3 (n=9) and 1.0 (n=7) mg/kg.

cle-treated group.

DISCUSSION

This study demonstrated that KR-32570, a newly synthesized inhibitor of the NHE-1, showed a potent antiarrhythmic effect against arrhythmia induced by focal ischemia and reperfusion in rats with potentially minimal hemodynamic effects.

The severity of reperfusion-induced arrhythmias is critically dependent on the duration of the proceeding period of ischemia. Thus, we selected a 10-min period of ischemia followed by 10-min period of reperfusion as it has been demonstrated that the incidence of fibrillation occurring upon reperfusion *in vivo* anesthetized rat reaches a peak 5-10 min after occlusion and subsides thereafter (Manning and Hearse, 1984) and our preliminary studies with different time schedule

Table II. Effects of KR-32570 on the alterations in mean arterial pressure (MAP) and heart rate (HR) induced by occlusion (10 min) and reperfusion (10 min) of the left anterior descending coronary artery in the anesthetized rat.

Parameter	KR-32570 (mg/kg)	Baseline	Administration	Occlusion (min)		Reperfusion (min)	
				5	10	5	10
MAP	Vehicle	93±5.4	109±3.8	102±5.8	104±6.3	106±4.7	101±4.1
(mmHg)	0.1	92±5.8	108±5.2	93±6.0	89±5.7	103±5.6	101±4.5
	0.3	96±5.1	119±4.7	105±5.8	101±5.8	100±5.6	97±5.3
	1.0	100±5.2	120±4.7	109±6.0	106±6.6	107±5.7	105±5.8
HR	Vehicle	368±12.7	352±11.0	366±10.7	340±8.4	366±12.3	379±9.0
(beats/min)	0.1	354±16.3	328±13.6	331±14.2	319±13.3	323±14.8	334±18.5
	0.3	342±21.9	330±21.5	352±26.2	351±28.1	346±17.2	322±15.0
	1.0	373±10.3	350±9.8	368±6.1	376±7.1	369±9.7	349±13.4

Values are mean±S.E.M. (n=7-11).

also showed the similar result. In the present study, KR-32570 significantly decreased ischemia-induced arrhythmia, such as PVC, VT and VF, at all doses tested. Moreover, KR-32570 significantly delayed onset time of PVC and VT occurring after occlusion of coronary artery. It has been known that ischemia-induced arrhythmias present two different phases; an early phase (phase 1a) and a late phase (phase 1b) of arrhythmias (Kaplinsky *et al.*, 1979). An early phase is characterized by a rapid increase of extracellular potassium concentration and a plateau between 0 and 10 min, and a late phase characterized by a slowly increasing after 15 to 30 min (Hill and Gettes, 1980; Hirche *et al.*, 1980). This increase of extracellular potassium concentration has known to be obtained via K^+ efflux through a sarcolemmal K_{ATP} channel rather than Na^+-K^+ pump (Bollensdorff *et al.*, 2004). The extracellular K^+ accumulation even mirrors that of the intracellular Na^+ accumulation, and the intracellular Na^+ accumulation results in intracellular Ca^{2+} accumulation (Fiolet *et al.*, 1984). This result may suggest that KR-32570 inhibited phase 1a arrhythmias occurring after occlusion of coronary artery via inhibition of an increase of extracellular potassium concentration in addition to the inhibition of NHE-1, although it remains to be elucidated.

Similarly to ischemia-induced arrhythmia, KR-32570 significantly decreased reperfusion-induced arrhythmia also including PVC, VT and VF. Moreover, KR-32570 dose dependently decreased the incidence of mortality occurring after reperfusion.

It has been reported that reperfusion-induced arrhythmia might be involved in increased automaticity secondary to the increase of intracellular Ca^{2+} that produces during ischemia and reperfusion (Tani and Neely, 1989). At reperfusion, the rapid washout of extracellular H^+ reactivates the NHE-1 resulting in an increase in intracellular Na^+. The elevation of intracellular Na^+ concentration can subsequently activate Ca^{2+} entry through the reverse mode of Na^+/Ca^{2+} exchanger, causing Ca^{2+} overload and cell damage (Doggrell and Hancox, 2003; Masereel et al., 2003). Thus, Na^+ influx via the NHE-1 after ischemia and reperfusion may be a critical trigger for cardiac injury and arrhythmia. Therefore, NHE-1 inhibitors may be effective in limiting the rapid intracellular Na^+ accumulation during reperfusion. Actually, a number of studies have suggested that NHE-1 inhibition could decrease reperfusion-induced arrhythmias in anesthetized dogs and rats (Aye et al., 1997; Ohara *et al.*, 1999; Zhu et al., 2002). In our previous studies, KR-32570 has about 20 times more strongly inhibited Na^+/H^+ exchange activity than cariporide, known as a potent and selective inhibitor of NHE-1, in PS120/NHE-1 cells (Lee *et al.*, 2005). Therefore, the effect of KR-32570 administered on ischemia/reperfusion-induced arrhythmia may be due to suppression of the intracellular Ca^{2+} overload, which is a conceivable consequence of inhibition of the NHE-1 after ischemia and reperfusion. In our previous studies, KR-32570 has significantly improved cardiac function in isolated rat heart preparations (Lee *et al.*, 2005) and tremendously reduced the myocardial infarction induced by ischemia and reperfusion in rats and dogs (unpublished data). These results suggest that in addition to acting as a cardioprotecive effect, KR-32570 has an antiarrhythmic effect. Furthermore, KR-32570 has shown a slow dissociation pattern in kinetic study with PS120/NHE-1 cells indicating that inhibition of NHE-1 has been persisted even after rinsing out of KR-32570 (personal communication with Dr. M. K. Lee, Yonsei University, Korea). This long-lasting inhibitory effect on NHE-1 has not been observed in other NHE-1 inhibitors. The unique phenomenon of KR-32570 with different kinetic profiles of other NHE-1 inhibitors might be helpful for obtaining better results with *in vivo* animal studies or clinical tests.

In conclusion, the results of the present study indicate that KR-32570 significantly decreased ischemia- and reperfusion-induced arrhythmia including PVC, VT and VF, and mortality in anesthetized rats. These results suggest that KR-32570 could be potentially useful to prevent lethal ventricular arrhythmias under such clinical conditions.

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