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Effects of SEA0400, a novel inhibitor of the Na^+/Ca^{2+} exchanger, on myocardial stunning in anesthetized dogs

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Abstract

Activation of the Na^+/Ca^{2+} exchanger may contribute to Ca^{2+} overload during reperfusion after transient ischemia. We examined the effects of 2-[4-[(2,5-difluorophenyl) methoxy]phenoxy]-5-ethoxyaniline (SEA0400), a selective inhibitor of Na^+/Ca^{2+} exchange, on a canine model of ischemia/reperfusion injury (myocardial stunning). Myocardial stunning was induced by a 15-min occlusion of the left anterior descending coronary artery followed by a 4-h reperfusion in anesthetized open-chest dogs. Reperfusion gradually restored myocardial percent segment shortening but remained depressed during a 4-h reperfusion period. A bolus intravenous injection of SEA0400 (0.3 or 1.0 mg/kg), given 1 min before reperfusion, improved significantly the recovery of percent segment shortening in the ischemic/reperfused myocardium. SEA0400 did not affect the hemodynamics and electrocardiogram parameters. In addition, SEA0400 did not affect reperfusion-induced change in coronary blood flow. These results suggest that the Na^+/Ca^{2+} exchanger is involved in the stunned myocardium of dogs after reperfusion, and that SEA0400 has a protective effect against myocardial stunning in dogs.

Keywords: Na^+/Ca^{2+} exchanger; SEA0400; Myocardial stunning

1. Introduction

The Na^+/Ca^{2+} exchanger plays an important role in the regulation of intracellular Ca^{2+} levels via the forward mode (Ca^{2+} extrusion) or reverse mode (Ca^{2+} influx) in excitable cells (Hryshko and Philipson, 1997; Matsuda et al., 1997). The Na^+/Ca^{2+} exchanger is the major mechanism of Ca^{2+} extrusion from cardiac myocytes during the normal action potential (Barry and Bridge, 1993). However, under ischemic conditions, intracellular Na^+ concentration ($[Na^+]_i$) is markedly increased by both the activated Na^+ influx via Na^+/H^+ exchange and the suppressed Na^+ extrusion via the Na^+/K^+ ATPase (Lazdunski et al., 1985). Several reports suggest that $[Na^+]_i$ accumulation may activate the Na^+/Ca^{2+} exchanger during reperfusion, resulting in an intracellular Ca^{2+} overload leading to various pathological conditions (Lederer et al., 1990).

"Myocardial stunning" is defined as prolonged myocardial contractile dysfunction observed after reperfusion following brief ischemia, without cell necrosis (Braunwald and Kloner, 1982). This phenomenon has been observed in several clinical situations, including after percutaneous transluminal coronary angioplasty, unstable angina, exercise/stress-induced ischemia, after thrombolysis, and after cardiopulmonary bypass (Bolli, 1992). Previous studies using the isolated perfused rat heart suggest that $[Na^+]_i$ accumulation during ischemia induces Ca^{2+} influx during reperfusion via the reverse mode of Na^+/Ca^{2+} exchange and the Ca^{2+} influx plays a critical role in determining the

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degree of functional recovery (Tani and Neely, 1989). This idea is supported by the fact that reduction of $[Na^+]_i$ accumulation by Na^+/H^+ exchange inhibitors attenuates post-ischemic contractile dysfunction (Karmazyn, 1988; Hendrikx et al., 1994; An et al., 2001). In the dog, a period of coronary occlusion lasting less than 20 min does not result in myocardial necrosis, yet nevertheless produces prolonged abnormalities of contractile performance (Kloner et al., 1983). This is a common model used in preclinical studies on myocardial stunning. Smart et al. (1997) reported that intracoronary infusions of amiloride improved the function of the stunned myocardium in open chest dogs. However, amiloride is not a selective Na^+/Ca^{2+} exchange inhibitor and can block Na^+/H^+ exchange, Na^+/K^+ ATPase and Ca^{2+}, Na^+ and K^+ channels (Bielefeld et al., 1986; Pierce et al., 1993). It is not known whether inhibition of Na^+/Ca^{2+} exchange could prevent myocardial stunning in vivo.

2-[4-[(2,5-Difluorophenyl)methoxy]phenoxy]-5-ethoxyaniline (SEA0400) has been characterized as the most potent inhibitor of Na^+/Ca^{2+} exchange in cultured neurons, astrocytes, microglia, cardiac sarcolemmal vesicles and rat cardiomyocytes (Matsuda et al., 2001; Takahashi et al., 2003). We also reported that SEA0400 at a concentration, which inhibited the Na^+/Ca^{2+} exchanger, had no significant effects on ion transporters (Na^+/H^+ exchange, Na^+/K^+ ATPase, Ca^{2+} ATPase), ion channels (Ca^{2+}, Na^+ and K^+ channels), 15 receptors including adrenergic and adenosine receptors, and 5 enzymes including phospholipase A_2 and phospholipase C (Matsuda et al., 2001). Furthermore, we demonstrated that SEA0400 protected the rat myocardium from ischemia/reperfusion injury in isolated Langendorff-perfused hearts (Takahashi et al., 2003). To elucidate the pathophysiological roles of the Na^+/Ca^{2+} exchanger in more clinically relevant animal models, we examined the effect of SEA0400, the most potent and selective inhibitor of Na^+/Ca^{2+} exchange known, on ischemia/reperfusion-induced myocardial stunning in anesthetized dogs.

2. Material and methods

All studies reported here have been reviewed by the Taisho Pharmaceutical. Animal Care Committee and have met the Japanese Experimental Animal Research Association Standards as defined in the Guidelines for Animal Experiments (1987).

2.1. Preparations

Laboratory dogs (LSG, Tokyo, Japan, 15–22 kg) of either sex were anesthetized with sodium pentobarbital (25 mg/kg i.v.) and ventilated with a positive-pressure respirator. The right femoral artery was cannulated for measurement of aortic blood pressure, and another catheter was placed in the right femoral vein for drug administration. Left thoracotomy was performed in the fourth intercostal space, and the pericardium was opened. A 7-fr solid-state catheter-tip pressure transducer (PC350, Millar Instruments, Houston, TX) was inserted into the left ventricular cavity through the left auricular appendage to measure left ventricular pressure. For measurement of regional myocardial length, two pairs of miniature piezoelectric crystals (5 MHz, Murata Manufacturing, Kyoto, Japan) were inserted into the subendocardial portion in the regions perfused by the left anterior descending coronary artery and by the left circumflex coronary artery. The crystals in each pair were separated by 8 to 12 mm. The left anterior descending coronary flow was measured using a precalibrated extracorporeal electromagnetic flow probe (Nihon Koden MF-26; inner diameter, 3 mm). A 5/0 braided silk suture was placed around the left anterior descending coronary artery. After stabilization for 30 min, coronary artery was occluded by pulling on the suture for 15 min.

2.2. Measurements of hemodynamics and myocardial percent segment shortening

Mean aortic blood pressure was measured via a catheter inserted in the femoral artery using a strain gauge transducer (Statham P23 Db). Heart rate was counted and monitored by a cardiotachometer triggered by aortic pulsation. Left ventricular (LV) pressure was measured using a solid-state catheter-tip pressure transducer, and the maximum first derivative of left ventricular pressure (+LVdp/dt) was obtained by electronic differentiation. Coronary blood flow was measured using a square-wave electromagnetic flowmeter (Nihon-Koden). The zero-level signal was obtained both in normal saline solution and during coronary occlusion. There was no significant shift in the zero level between calibration in saline and that in situ. Mean aortic blood pressure and mean coronary blood flow were obtained with a 2-s time constant. The electrocardiogram (ECG) was recorded from standard limb lead II. The QTc interval was calculated using Fredericia's formula, $QTc=QT/(RR)^{1/3}$. Systolic segment length was measured at 20 ms before the peak negative LVdp/dt, and diastolic segment length was measured at the onset of rapid upstroke of positive LVdp/dt. The segment length data were normalized by use of a value of 10.0 for the pre-ischemic diastolic segment length (Theroux et al., 1974). Percent segment shortening was calculated by the formula: [(diastolic segment length−systolic segment length)/diastolic segment length]×100. An average value of at least five beats was used for later analysis. To minimize differences among animals, percent segment shortening was normalized as a percentage of pre-ischemic baseline values. All variables were monitored using a Thermal array recorder RTA-3100 (Nihon-Koden Polygraph System) for later analysis.

2.3. Experimental protocol

Dogs were randomly assigned to one of three treatment groups: (a) vehicle for SEA0400 (a lipid emulsion, n=8); (b)

SEA0400 (0.3 mg/kg, n=7); (c) SEA0400 (1 mg/kg, n=8). The experiments were begun >30 min after connecting and calibrating the instrumentation, by which time all variables had become stable. After control measurements of hemodynamics and segment shortening, the left anterior descending coronary artery was occluded by pulling on the suture for 15 min. Vehicle or SEA0400 was administered intravenously 1 min before reperfusion. For reperfusion, we released the suture and reperfusion was confirmed by an increase in the left anterior descending coronary flow. Hemodynamics and segment shortening were determined every 5 min for the first 30 min of reperfusion and every 15 min for up to 4 h of reperfusion. Values at each time point were the average of three to five consecutive arrhythmia-free cardiac cycles.

2.4. Statistical analysis

Data are expressed as the means±S.E.M. For statistical analysis, we used a two-way analysis of variance for repeated measurements, and Dunnett's significant difference test was used to determine which individual means differed when an overall difference was detected. Values of $P<0.05$ were considered to be significant.

2.5. Drugs

SEA0400 was synthesized in Taisho Pharmaceutical (Saitama, Japan). SEA0400 was administrated as a lipid emulsion containing 10% soybean oil. The dosage of SEA0400 was based on the tissue concentration, which was sufficient to inhibit the Na^+/Ca^{2+} exchanger, in our preliminary study.

3. Results

Initially, 26 dogs were instrumented in the study; however, 3 dogs were excluded due to ventricular fibrillation during reperfusion (vehicle-treated group, 2 dogs; 1 mg/kg of SEA0400-treated group, 1 dog). Thus, a total of 23 dogs were included in data analysis: 8 in the vehicle-treated dogs, 7 in the 0.3 mg/kg of SEA0400-treated dogs and 8 in the 1.0 mg/kg of SEA0400-treated dogs. The hemodynamics, segment length data and ECG parameters of vehicle- and SEA0400-treated dogs during preocclusion, occlusion and 4 h of reperfusion are summarized in Table 1. There were no significant differences in mean arterial blood

Table 1
Hemodynamics, segment length and ECG parameters

	MBP (mm Hg)	HR (bpm)	LVSP (mm Hg)	LVEDP (mm Hg)	LVdp/dt (mm Hg/s)	EDL (mm)	ESL (mm)	PQ (ms)	QRS (ms)	QTc (ms)
Preocclusion										
Vehicle	119±6	128±4	128±4	8±2	1900±170	10.0	8.89±0.1	96±8	62±2	258±6
SEA 0.3 mg/kg	123±5	131±4	134±7	8±1	1800±70	10.0	8.75±0.1	95±6	60±3	255±6
SEA 1 mg/kg	127±6	136±8	135±3	8±1	2000±100	10.0	8.93±0.1	103±6	59±3	248±9
Occlusion (15 min)										
Vehicle	122±4	121±5	130±2	11±2	1700±140	11.15±0.4	11.61±0.5	98±7	62±2	251±6
SEA 0.3 mg/kg	122±5	125±6	130±4	11±1	1600±60	10.95±0.2	11.56±0.4	98±6	61±1	242±7
SEA 1 mg/kg	127±6	128±8	132±6	12±1	1800±50	10.94±0.2	11.52±0.3	101±6	57±3	243±5
Reperfusion (60 min)										
Vehicle	133±4	137±6	141±5	10±2	1800±130	10.83±0.4	10.47±0.4	99±9	67±1	253±7
SEA 0.3 mg/kg	129±5	126±5	138±6	9±1	1700±80	10.27±0.2	9.44±0.2*	99±6	59±4	258±7
SEA 1 mg/kg	130±4	138±7	140±6	9±1	2000±70	10.32±0.1	9.57±0.2*	95±4	63±3	257±11
Reperfusion (120 min)										
Vehicle	133±4	140±7	142±5	9±2	1800±150	11.01±0.4	10.57±0.4	94±10	66±1	261±4
SEA 0.3 mg/kg	136±4	131±6	145±6	7±1	1700±90	10.31±0.2*	9.51±0.2*	94±7	56±4	255±8
SEA 1 mg/kg	130±5	142±8	137±4	8±1	1900±80	10.18±0.1*	9.38±0.1*	99±6	56±3	255±9
Reperfusion (180 min)										
Vehicle	134±5	141±6	142±6	9±2	1800±180	10.85±0.4	10.29±0.4	97±9	65±2	265±7
SEA 0.3 mg/kg	137±6	129±6	146±6	8±2	1700±70	10.19±0.2*	9.36±0.2*	97±4	56±3	267±12
SEA 1 mg/kg	132±3	145±7	141±5	7±1	2000±80	10.09±0.1*	9.29±0.1*	96±4	62±3	247±11
Reperfusion (240 min)										
Vehicle	134±4	142±8	145±7	8±2	1800±130	10.58±0.3	10.15±0.3	94±10	67±1	263±9
SEA 0.3 mg/kg	137±4	131±6	147±5	7±1	1700±80	10.10±0.1*	9.26±0.2*	98±4	57±4	260±8
SEA 1 mg/kg	128±3	142±8	138±5	7±1	1800±90	10.14±0.1*	9.31±0.1*	96±5	60±4	250±13

SEA, SEA0400; MBP, mean arterial blood pressure; HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVdp/dt, maximal rate of left ventricular pressure rise; DL and SL, diastolic and systolic segment length within the ischemic region; ECG, electrocardiogram. Values are mean±S.E.M.

* $P<0.05$ compared with vehicle.

pressure, heart rate, LV systolic pressure, LV end-diastolic pressure, LVdp/dt or ECG parameters within or between groups. Diastolic segment length and systolic segment length within the ischemic/reperfused region were significantly reduced by 0.3 and 1.0 mg/kg of SEA0400 when compared to vehicle-treated dogs. Changes in left anterior descending coronary blood flow of vehicle- and SEA0400-treated dogs during ischemia and reperfusion are illustrated in Fig. 1(A). Coronary blood flow decreased to 0 ml/min during occlusion and hyperemic flow was observed after start of reperfusion in all groups. Changes in coronary blood flow were not modified by SEA0400. Effects of SEA0400 on percent segment shortening in the nonischemic and ischemic/reperfused region are shown in Fig. 1(B and C). In the nonischemic region, there were no significant differences in percent segment shortening within or between groups. During occlusion, percent segment shortening of the ischemic/reperfused region decreased rapidly and became negative in all groups. After reperfusion, percent segment shortening recovered from a negative value to about 35% of the baseline value in the vehicle-treated groups. SEA0400, given at 0.3 mg/kg and 1 mg/kg i.v. bolus 1 min before reperfusion, improved significantly the recovery of percent segment shortening from 35.8±8.6% (vehicle), when estimated based on the area under curve (AUC), to 64.7±5.8% and 71.6±8.2%, respectively.

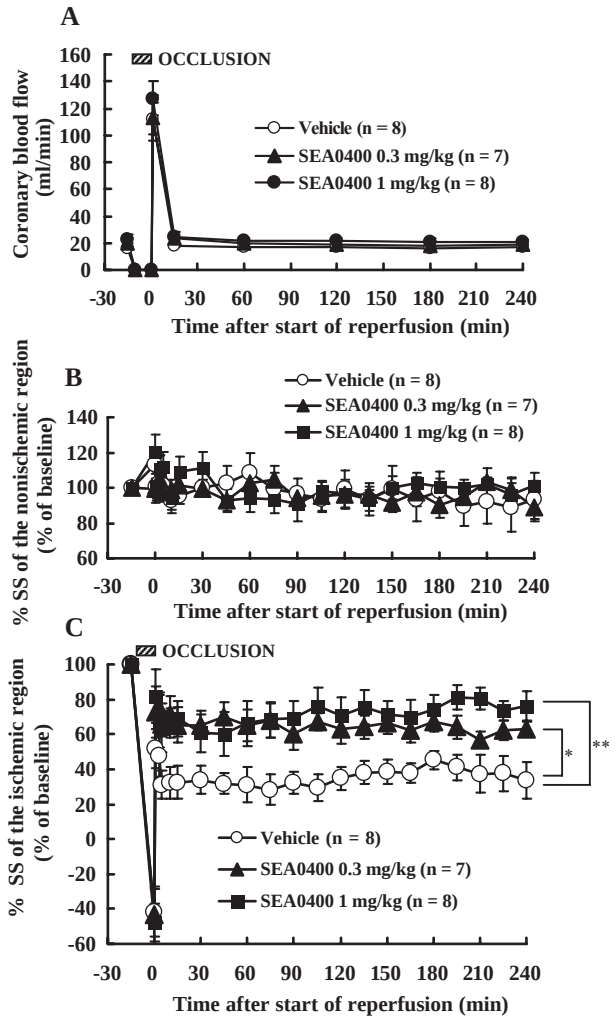

Fig. 1. Effects of SEA0400 on changes in coronary blood flow (A) and percent segment shortening (B and C) during ischemia/reperfusion in anesthetized dogs. Percent segment shortening (%SS) is expressed as a percentage of the pre-ischemic baseline data. SEA0400 (0.3 or 1.0 mg/kg) was administered intravenously 1 min before reperfusion. Each group consisted of seven to eight different dogs. Values are means±S.E.M. *P<0.05 and **P<0.01 compared with vehicle.

4. Discussion

The present study shows for the first time that SEA0400, a novel and selective Na^+/Ca^{2+} exchange inhibitor, improves myocardial stunning during reperfusion in dogs in vivo. These results indicate that the Na^+/Ca^{2+} exchanger plays an important role in the stunned myocardium of dogs after reperfusion. This study extends the findings obtained in isolated rat or rabbit hearts (Magee et al., 2003; Takahashi et al., 2003) to another species in a clinically relevant preparation. Because pharmacological interventions given prior to ischemia are not always feasible in the clinical setting, SEA0400 was administered just prior to reperfusion in the present study. Na^+/Ca^{2+} exchange inhibition may prove to be efficacious adjunct therapy for current reperfusion strategies.

Although the mechanisms related to ischemia/reperfusion injury are complicated, previous in vitro studies suggest that Ca^{2+} influx via the reverse mode of Na^+/Ca^{2+} exchange during reperfusion is important to produce Ca^{2+} overload, causing myocardial stunning (Cross et al., 1998; Murphy et al., 1991; Tani and Neely, 1989). Furthermore, in vivo studies using non-selective blockers (Smart et al., 1997) or ionic manipulations (Hori et al., 1991) revealed that the inhibition of Na^+/Ca^{2+} exchange could improve the cardiac function of the stunned myocardium in dogs. 2-[2-[4-(4-Nitrobenzyloxy)phenyl]ethyl]isothiourea (KB-R7943), a relatively specific inhibitor of Na^+/Ca^{2+} exchange, prevented ischemia/reperfusion-induced myocardial contractile dysfunction in the isolated perfused rat heart (Inserte et al., 2002), while it did not suppress ischemia/reperfusion-induced arrhythmias in anesthetized rats or dogs (Lu et al., 1999; Miyamoto et al., 2002). The apparent discrepancy may be due to lack of specificity of the inhibitor for the Na^+/Ca^{2+} exchanger. KB-R7943 inhibits other ion transport systems, such as Na^+/H^+ exchange, Ca^{2+}, Na^+ and K^+ channels (Arakawa et al., 2000; Matsuda et al., 2001) and it also influences arterial blood pressure and heart rate in anesthetized dogs (Miyamoto et al., 2002). To our knowledge, the effects of KB-R7943 on in vivo myocardial stunning have not yet been reported. We found that our newly synthesized compound, SEA0400, is the most potent and selective inhibitor of Na^+/Ca^{2+} exchange reported to date (Matsuda et al., 2001). The potency of SEA0400 was

about 100 times that of KB-R7943 and SEA0400 did not significantly affect the other 32 proteins examined (Matsuda et al., 2001). We also demonstrated previously that SEA0400 had a protective effect against ischemia/reperfusion arrhythmias in anesthetized rats (Takahashi et al., 2003). Therefore, SEA0400 is a valuable drug tool for studies on the pathophysiological roles of the Na^+/Ca^{2+} exchanger in in vivo animal models.

Positive inotropic intervention can enhance the functional recovery of the stunned myocardium (Kloner and Jennings, 2001). Since there were no significant differences in percent segment shortening of the nonischemic region between the vehicle- and SEA0400-treated dogs, SEA0400 itself had no direct effect on myocardial contractility. In addition, SEA0400 did not affect the heart rate-left ventricular systolic pressure product, an index of myocardial oxygen demand, within or between groups throughout the experiment (data not shown). Thus, the improvement of contractile dysfunction by SEA0400 was probably not caused by the result of its direct inotropic effects on the stunned myocardium.

Ca^{2+} antagonists were shown to improve the cardiac function of the stunned myocardium in canine models (Lamping and Gross, 1985; Przyklenk and Kloner, 1991). The beneficial effects on the stunned myocardium may be due in part to afterload reduction and, to vasodilatory properties of Ca^{2+} antagonists. In the present study, administration of SEA0400 was without effect on aortic blood pressure, heart rate, coronary blood flow, LVdp/dt and ECG parameters throughout the experimental periods. These results suggest that cardioprotective effects of SEA0400 were independent of the hemodynamics and these effects may be due to Na^+/Ca^{2+} exchange inhibition.

Previous studies using the isolated perfused rat heart suggest that the development of myocardial stunning can be related to cytosolic calcium overload at the onset of reperfusion (Du Toit and Opie, 1992; Imahashi et al., 1999). We previously demonstrated that SEA0400 protected the rat myocardium from ischemia/reperfusion injury in isolated Langendorff-perfused hearts (Takahashi et al., 2003). In this study, the treatment was given only during the early reperfusion period (first 10 min). This result supports the hypothesis that Ca influx via Na^+/Ca^{2+} exchange during the early phase of reperfusion plays a critical role in determining the degree of functional recovery. Although we did not determined the plasma concentrations for SEA0400 in the present study, our preliminary study has shown that the plasma concentrations in dogs are 0.11 ± 0.02 and 0.32 ± 0.11 μg/ml at 30 min after intravenous administration with 0.3 and 1 mg/kg, respectively. These correspond to 0.29 and 0.87 μM, hence sufficient concentrations to inhibit the Na^+/Ca^{2+} exchanger. Therefore, we suggest that a single bolus intravenous injection of SEA0400 (0.3 or 1.0 mg/kg) can inhibit cytosolic calcium overload via Na^+/Ca^{2+} exchange during the early phase of reperfusion.

There is the evidence in the isolated perfused rat heart that $[Na^+]_i$ increases after 15 min of ischemia (Imahashi et al., 1999; Tani and Neely, 1989). Although we did not measure myocardial $[Na^+]_i$, previous studies have demonstrated that the myocardial pH decreased after 15 min occlusion of coronary artery in anesthetized dogs (Aihara et al., 2001; Ichihara et al., 1984). Increased intracellular H^+ concentration during ischemia is believed to activate the Na^+/H^+ exchanger (Lazdunski et al., 1985). Therefore, the activated Na^+ influx via Na^+/H^+ exchange may promote Ca^{2+} influx via the reverse-mode of Na^+/Ca^{2+} exchange in this canine stunning model.

In conclusion, the results of the present study demonstrate that SEA0400 improves the dysfunction of the stunned myocardium after reperfusion to dogs in vivo. The present findings using the specific Na^+/Ca^{2+} exchange inhibitor SEA0400 suggest that activation of the Na^+/Ca^{2+} exchanger is involved in the canine stunned myocardium after reperfusion.

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