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Abnormal response to ryanodine in oesophageal striated muscle of spontaneously hypertensive rats

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Abstract

The effects of ryanodine on twitch contraction and basal tension of oesophageal striated muscle were compared between preparations from stroke-prone spontaneously hypertensive rats (SHRSP) and normotensive Wistar Kyoto rats (WKY). Ryanodine (3×10^{-7} M) augmented the twitch contraction in WKY preparations, butt attenuated it in SHRSP preparations. Rates of contraction and relaxation of twitch contraction, normalized to developed tension, were slightly decreased by ryanodine in both preparations. The effect of ryanodine was not different between WKY and SHRSP preparations. Ryanodine elevated the basal tension in WKY preparations but not in SHRSP preparations. Ryanodine elevated the intracellular Ca^{2+} level in both preparations, but the response was significantly less in SHRSP preparations. Resting and action potentials were not significantly different between WKY and SHRSP preparations, while the duration of the action potential was significantly longer in SHRSP preparations. Ryanodine did not alter the resting and action potentials of either preparation. These results suggest that the Ca^{2+} handling properties, including the ryanodine receptor, of the sarcoplasmic reticulum are genetically altered in oesophageal striated muscle of SHRSP.

Keywords: Ryanodine; Oesophageal striated muscle; Sarcoplasmic reticulum; (SHRSP) Stroke-prone spontaneously hypertensive rat; Twitch contraction

1. Introduction

Changes in excitation and contraction including intracellular Ca^{2+} handling have been reported in vascular smooth muscle of hypertensive animals (Moriyama et al., 1989; Sugiyama et al., 1990; Kanagy et al., 1994; see Kwan, 1985; see also Postnov and Orlov, 1985). These changes may be the cause or the result of hypertension. Such changes have been reported not only in vascular but also in visceral smooth muscle (Altman, 1977; Kwan et al., 1982). However, there have been relatively few investigations of striated muscle (Carlsen and Gray, 1987; Syme et al., 1990; Gray et al., 1994a,b; Bachir-Lamrini et al., 1990; Ameen et al., 1991), because these muscles are thought to contribute less to the initiation or maintenance of hypertension.

The outer layer of the oesophagus is composed of striated muscle, hence it may be classified as a visceral striated muscle. We have reported that the effects of cyclopiazonic acid, known to act directly on the sarcoplasmic reticulum of striated muscle (Goeger and Riley, 1989; Seidler et al., 1989; Kurebayashi and Ogawa, 1991), are markedly less pronounced in the oesophageal striated muscle of stroke-prone spontaneously hypertensive rats (SHRSP) (Sekiguchi et al., 1999). In addition, Bortolotto et al. (2001) have recently reported that the sensitivity to caffeine, which acts directly on the sarcoplasmic reticulum (Delay et al., 1986; Konishi and Kurihara, 1987), is altered in the soleus muscle of spontaneously hypertensive rats (SHR). More recently, we have also reported that the effects of caffeine are less pronounced in preparations from SHRSP (Sekiguchi et al., 2003). These results indicate that the properties of the sarcoplasmic reticulum, particularly the caffeine receptor, may be altered in striated muscle from SHRSP.

Ryanodine also acts directly on the ryanodine receptor of the sarcoplasmic reticulum and fixes Ca^{2+}-release channels in an open state (Imagawa et al., 1987; Fryer et al., 1989; Lamb and Stephenson, 1990; Oyamada et al., 1993; see also Meissner, 1994). Ca^{2+}-release channels are also sensitive to caffeine (Sitsapesan and Williams, 1990). In this context, ryanodine is often used for studying the excitation–contrac-

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tion coupling of striated muscle (see Meissner, 1994; see also Ríos and Pizarro, 1991; Ebashi, 1991).

In the present experiments, the effects of ryanodine on twitch contractions and basal tension of oesophageal striated muscle were studied and compared in preparations from normotensive Wistar Kyoto rats (WKY) and SHRSP.

2. Materials and methods

2.1. Animals and measurement of blood pressure

Rats were handled according to the "Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences" of the Physiological Society of Japan.

Male 16-week-old SHRSP and age-matched WKY were used in the present experiments. These rats were purchased from Shimizu Laboratory Supplies (Kyoto, Japan) at the age of 4 weeks and kept in our animal facility under conditions of constant temperature of 22 °C, humidity of 60% and light and dark cycle of 12 h until they were killed. They had free access to normal chow (SP, Funabashi, Japan) and tap water. The blood pressure of these rats was measured by means of tail-cuff method. Prior to the measurement, the rats were warmed at 40 °C for 10 min to make the measurement easy and exact.

2.2. Preparations

The rats were killed by bleeding from the *vena cava* under anaesthesia with CO_2. After the blood was removed by infusing modified Tyrode's solution described below from the left ventricle, the oesophagus was excised from the thoracic cavity and immersed in modified Tyrode's solution. Fat and connective tissue were removed carefully and longitudinal strips of 10-mm length and 2-mm width were made from the outer layer of the oesophagus and placed in modified Tyrode's solution.

The preparation was mounted on a plastic bar, which was inserted in an organ bath, with silk thread tied to one end of the preparation. The other end of the preparation was tied with thin tungsten wire of 30-μm diameter to a force-displacement transducer (Minevia, Nagano, Japan) so that contraction and relaxation could be measured isometrically. Organ baths of 10 ml were filled with modified Tyrode's solution kept at 37 °C by circulating warm water at the same temperature into the outer chamber of the organ bath.

Table 1
Systolic blood pressure and body weight of rats used in the present experiment

	Systolic blood pressure (mm Hg)	Body weight (g)
WKY (n=10)	141.2±2.3	370.0±8.6
SHRSP (n=10)	233.2±5.9[a]	260.3±13.0[a]

[a] $P<0.001$ vs. WKY.

Table 2
Properties of twitch contraction in the oesophageal striated muscles from WKY and SHRSP

	WKY (n=13)	SHRSP (n=8)
Amplitude (mN)	2.5±0.5	2.5±0.5
Rate of contraction (mN/s)	50.5±11.2	61.7±14.6
Rate of relaxation (mN/s)	40.0±8.7	48.0±11.1
Normalized rate of contraction	32.3±1.1	32.6±0.9
Normalized rate of relaxation	23.9±0.9	25.7±1.1
Time to peak (s)	61.3±1.2	60.8±1.4
80% relaxation time (s)	48.3±0.9	46.9±2.1

2.3. Solutions

The composition of the modified Tyrode's solution was as follows (mM): NaCl, 137; KCl, 5.4; $CaCl_2$, 2.0; $MgCl_2$, 1.0; $NaHCO_3$, 11.9; NaH_2PO_4, 0.4; glucose, 5.6; equilibrated with a gas mixture of 95% O_2 and 5% CO_2. The pH of the solution at 37 °C was 7.3. K-Tyrode's solution containing 142.4 mM KCl was made by replacing all NaCl in the Tyrode's solution with KCl.

2.4. Measurement of twitch contraction

Twitch contraction was recorded isometrically using a force-displacement transducer (Minevia, Nagano, Japan). The preparation was stimulated with electric pulses through two platinum wire electrodes placed close to each side of the preparation in the presence of 10^{-6} M *d*-tubocurarine, to exclude the influence of the motor nerve (Gruber, 1968; Marsh and Bieger, 1987; Sekiguchi et al., 1999). Pulse duration and frequency of the electrical stimulation were 10 ms and 1/min, respectively. These values were determined according to previous reports (Sekiguchi et al., 1999). Electrical stimulation under this condition initiated twitch contractions of constant amplitude for at least 1 h. Rates of contraction and relaxation were recorded with a differential amplifier (NEC, Tokyo, Japan) and the values were normalized to the developed tension by dividing the rate by developed tension using a dividing amplifier (NEC-San-ei, Tokyo, Japan).

2.5. Measurement of intracellular Ca^{2+} level

The intracellular Ca^{2+} level ($[Ca^{2+}]_i$) was measured according to the method reported by Ozaki et al. (1987) with a fluorescent Ca^{2+} indicator fura-PE3. With fura-PE3, $[Ca^{2+}]_i$ can be measured without a significant decline in fluorescence for several hours (Kim et al., 1996). The rat oesophageal striated muscle preparations (1-mm width, 7-mm length) were treated with the acetoxymethyl ester (AM) of fura-PE3 (20 μM) for 4 h at room temperature. Pluronic F-127 (0.06%) was added to increase the solubility of fura-PE3/AM. After being loaded, the preparations were washed with modified Tyrode's solution at 37 °C for 15 min to remove

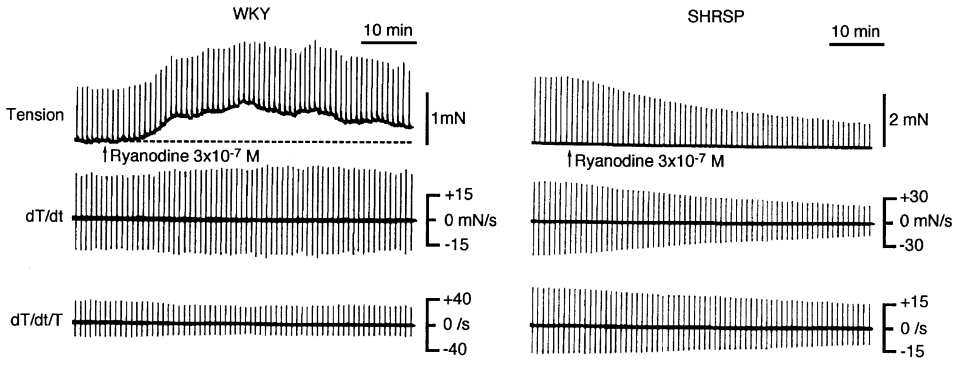

Fig. 1. Effects of 3×10^{-7} M ryanodine on twitch contraction and rates of contraction and relaxation of oesophageal striated muscle. Left, preparation from WKY. Right, preparation from SHRSP. Dotted line in the preparation from WKY indicates the basal level before the application of ryanodine. dT/dt, rates of contraction (upward) and relaxation (downward). dT/dt/T, rates of contraction (upward) and relaxation (downward) normalized by developed tension.

free fura-PE3/AM. Each preparation was held horizontally in a temperature-controlled organ bath (5 ml, 37 °C) connected at one end to a force-transducer. The preparations were illuminated by dual wavelength (340 and 380 nm) excitation light (128 Hz), and fluorescence emilted at 500 nm (F_{340} and F_{380}) was measured with a fluorometer (CAF-110, JASCO, Tokyo), and the ratio of F_{340} to F_{380} (F_{340}/F_{380}) was treated as an indicator of $[Ca^{2+}]_i$. The ratios obtained in Ca^{2+}-free Tyrode's solution containing 20 mM ethylene glycol-bis(β-aminoethyl-ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA) and in the presence of 142.4 mM K^+ were taken as 0 and 100%, respectively, and all other values were normalized using these two values.

2.6. Membrane potential

Resting and action potentials of the oesophageal striated muscle were measured using a glass microelectrode which had a tip resistance of 40–60 MΩ. The preparations were placed horizontally in an organ bath with a

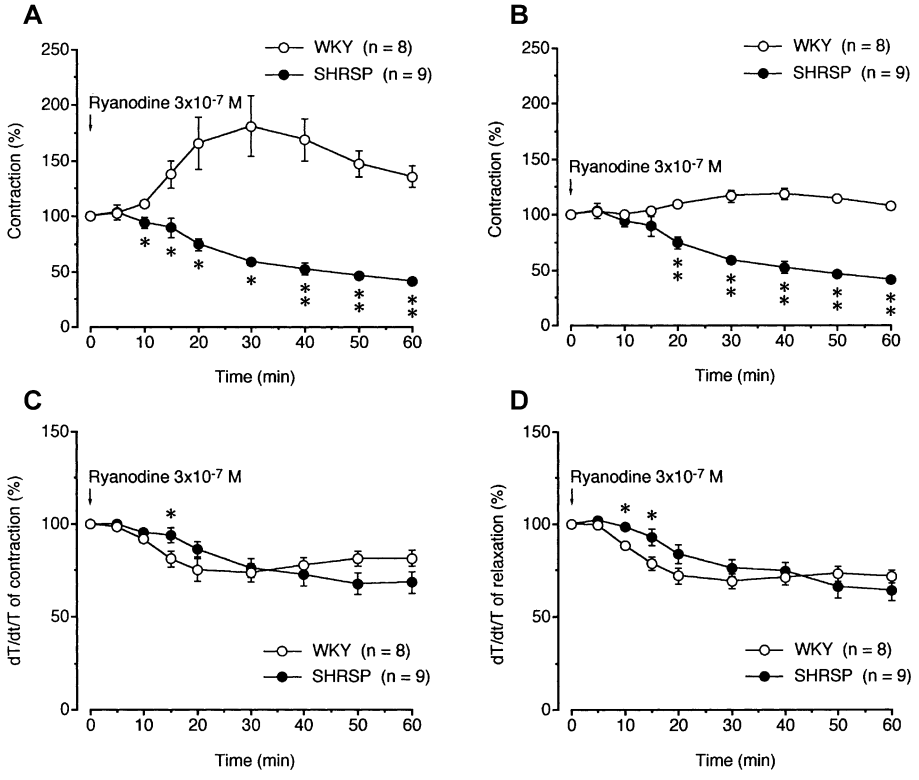

Fig. 2. Time-dependent changes in twitch contraction and normalized rates of twitch contraction and relaxation after the application of 3×10^{-7} M ryanodine. Changes are expressed as percentages of the respective value before the application of the drug. A, peak tension of the twitch contraction including elevated basal tension. B, peak tension subtracted from the elevated basal tension. C, normalized rate of contraction. D, normalized rate of relaxation.

volume of 1.5 ml and immersed under a constant flow (2.0 ml min^{-1}) of incubation medium at a constant temperature of 37 °C. The potential changes were amplified with a microelectrode amplifier (MEZ-8301, Nihon Kohden, Tokyo, Japan) and displayed on a digital oscilloscope (COR 5521, Kikusui, Kawasaki, Japan). The data were stored at an acquisition rate of 20 kHz using a PowerLab recording System (AD Instruments, New South Wales, Australia) on a computer (ThinkPad i1400, IBM, Armonk, NY, USA). A sudden drop in potential was regarded to reflect penetration of the electrode through the cell membrane, and the value after the potential achieved its stable level was taken as the resting potential. The action potentials were initiated by electrical pulses applied through two platinum wires placed close to the preparation. The electrical pulses were generated by an electrical stimulator (SEN-3301, Nihon Kohden). The duration of the pulses was 100 μs and the amplitude of the pulses was adjusted to a level just above the threshold for initiation of the action potential. The duration of the action potential was measured at the level of 70% repolarization from the top of the action potential. The effects of ryanodine were observed by adding the drug to the incubation medium.

2.7. Drugs

The following drugs were used: caffeine (Wako, Osaka, Japan), *d*-tubocurarine chloride (Sigma, St. Louis, MO, USA), EGTA (Dojindo, Kumamoto, Japan), fura-PE3/AM (Texas Fluorescence Laboratory, Austin, TX, USA), pluronic F-127 (Sigma) and ryanodine (Wako).

2.8. Statistics

Obtained values are expressed as means±S.E. and analysed by the Student's *t*-test and, when necessary, by two-way analysis of variance (ANOVA) with the Bonferroni/Dunn's post-hoc test. *P*-values less than 0.05 were considered to be significant differences.

3. Results

3.1. Body weight and blood pressure of the rats

Body weight and blood pressure of the rats are shown in Table 1. The body weight of SHRSP was significantly lower than that of WKY. The blood pressure of SHRSP was significantly higher than that of WKY.

3.2. Twitch contraction of oesophageal striated muscle from WKY and SHRSP

Electrical stimulation at the strength described in the Methods initiated twitch contraction of the preparations from both WKY and SHRSP. The amplitude of the twitch contraction was slightly but significantly greater in the preparations from SHRSP. Rates of contraction and relaxation were not significantly different, especially when they were normalized to developed tension. The time to peak tension and time to 80% relaxation were also not significantly different between these preparations; hence, the duration of twitch contraction was almost identical (Table 2).

3.3. Effects of ryanodine on twitch contraction

The twitch contraction was augmented by application of ryanodine at concentrations between 10^{-8} and 3×10^{-7} M in the preparations from WKY but was attenuated in preparations from SHRSP. Typical traces of the effect of 3×10^{-7} M ryanodine on twitch contraction in the preparations from WKY and SHRSP are shown in Fig. 1. Both rates of contraction and relaxation were decreased slightly by the same concentration of drug in both preparations when normalized to the developed tension (Fig. 2). Time to peak tension was not altered in the preparations from WKY and decreased in those from SHRSP (Fig. 3). Time to 80% relaxation was increased slightly in the preparations from WKY and was decreased in those from SHRSP

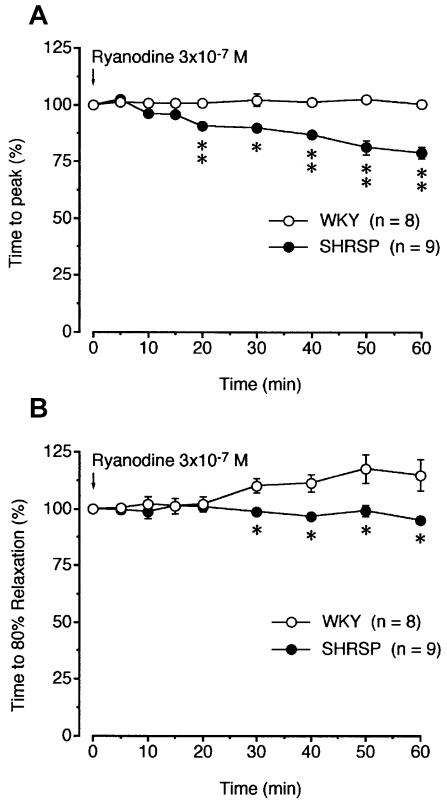

Fig. 3. Time-dependent changes in time to peak and 80% relaxation time of the twitch contraction. A, time to peak of the twitch contraction. B, time from peak to 80% relaxation. These data are expressed as a percentage of the value before the application of the drug.

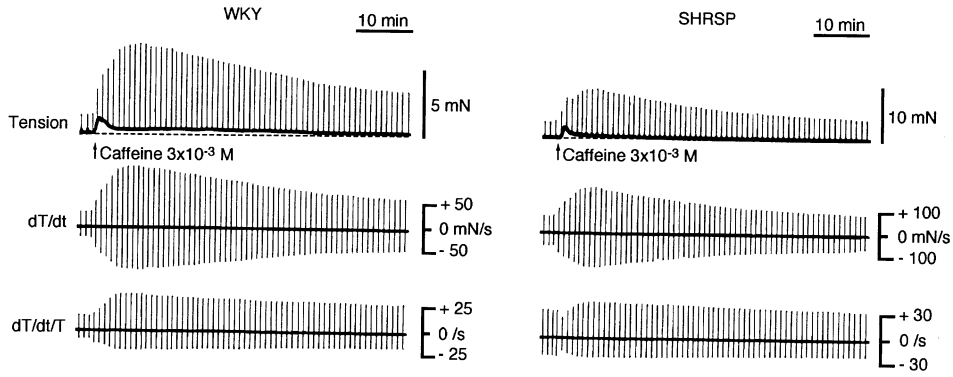

Fig. 4. Effects of 3×10^{-3} M caffeine on twitch contraction of oesophageal striated muscle. Left, preparation from WKY. Right, preparation from SHRSP. Note that caffeine at this concentration enhanced the twitch contraction in both preparations.

(Fig. 3). Thus, the duration of twitch contraction measured at the level of 80% relaxation was slightly increased by ryanodine in the preparations from WKY, while it was slightly decreased by the drug in the preparations from SHRSP.

The basal tension was elevated by ryanodine at concentrations higher than 10^{-7} M in a concentration-dependent manner in the preparations from WKY. In the preparations from SHRSP, no elevation of basal tension was induced by ryanodine at concentrations up to 3×10^{-7} M (Fig. 1).

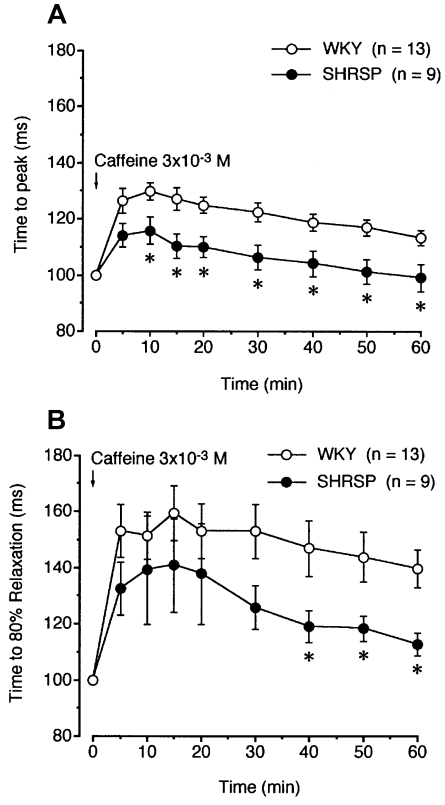

Fig. 5. Effects of 3×10^{-7} M caffeine on time to peak tension and 80% relaxation time. A, time to peak tension of the twitch contraction. B, time from peak tension to 80% relaxation. Other points are the same as in Fig. 3.

3.4. Comparative experiments with caffeine

Caffeine at 3×10^{-3} M augmented the twitch contraction in preparations from both WKY and SHRSP (Fig. 4). The augmentation of the twitch contraction was much less pronounced in the preparations from SHRSP than in the preparations from WKY. Both rates of contraction and relaxation of twitch contraction were increased in both preparations even after normalization to the developed tension (Fig. 5). Time to peak tension and time to 80% relaxation were increased, and thus the duration of the twitch contraction was prolonged. When the caffeine concentration was increased to 10^{-2} M, the rate of relaxation was markedly decreased, causing a marked prolongation of the duration of the twitch contraction (data not shown).

3.5. Effects of ryanodine on intracellular Ca^{2+} level ($[Ca^{2+}]_i$)

The basal $[Ca^{2+}]_i$ was slightly but significantly higher in the preparations from WKY than in those from SHRSP (Fig. 6). Changing the incubation medium from modified

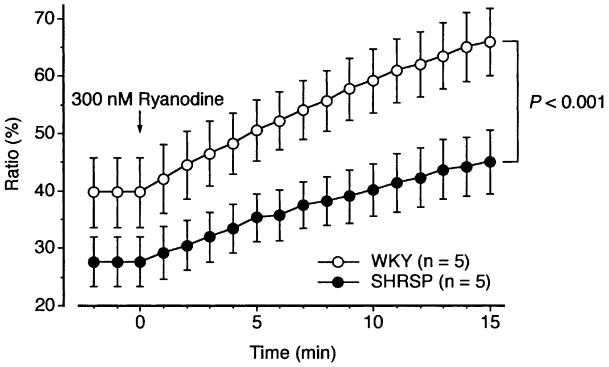

Fig. 6. Effect of 3×10^{-7} M ryanodine on the intracellular Ca^{2+} level in oesophageal striated muscle from WKY and SHRSP. The levels obtained by soaking preparations in Ca^{2+}-free Tyrode's solution containing 20 mM EGTA and those obtained by soaking K-Tyrode's solution in the presence of 2 mM Ca^{2+} were taken as 0% and 100%, respectively, as described in Section 2.

Table 3
Effects of ryanodine on resting and action potential, and duration of action potential

	Resting membrane potential (mV)	Action potential (mV)	Duration of action potential (ms)
WKY			
Control	−71.9±0.4 (*n*=55)	85.8±1.2 (*n*=24)	1.43±0.05 (*n*=24)
Ryanodine 100 nM	−71.0±0.3 (*n*=55)	88.7±1.6 (*n*=24)	1.53±0.05 (*n*=24)
Ryanodine 300 nM	−71.4±0.4 (*n*=56)	85.6±1.2 (*n*=24)	1.56±0.06 (*n*=24)
SHRSP			
Control	−71.9±0.6 (*n*=51)	90.5±2.4 (*n*=24)	2.34±0.13[a] (*n*=24)
Ryanodine 100 nM	−71.3±0.4 (*n*=51)	94.3±1.7[b] (*n*=25)	2.32±0.11[a] (*n*=25)
Ryanodine 300 nM	−70.9±0.5 (*n*=56)	97.0±2.2[a,c] (*n*=26)	2.32±0.10[a] (*n*=26)

[a] vs. WKY ($P<0.001$).
[b] vs. WKY ($P<0.05$).
[c] vs. Control ($P<0.05$).

Tyrode's to K-Tyrode's solution induced a transient elevation of $[Ca^{2+}]_i$ associated with a transient contraction in both preparations, which was taken as 100% in the present experiment (data not shown). The application of Ca^{2+}-free Tyrode's solution containing 20 mM EGTA caused a reduction in $[Ca^{2+}]_i$, and the reduced level was taken as 0 in the present experiment (data not shown). Application of ryanodine in normal Tyrode's solution caused a slow elevation of $[Ca^{2+}]_i$, although the elevation was much smaller than that caused by K-Tyrode's solution (100%) (Fig. 6). The elevation was significantly smaller in preparations from SHRSP.

3.6. Membrane potential and action potential

The resting potential of the oesophageal striated muscles was not significantly different between the preparations from WKY and SHRSP (Table 3). The amplitude and duration of the action potential were also not different between these preparations. Neither concentrations of 10^{-7} nor 3×10^{-7} M of ryanodine altered the resting and action potential of either preparation (Table 3).

4. Discussion

Ryanodine acts on the receptor of the Ca^{2+}-induced Ca^{2+}-release channel and locks the channel open (Imagawa et al., 1987; Lamb and Stephenson, 1990; Oyamada et al., 1993; see also Meissner, 1996), which leads to an increase in the intracellular Ca^{2+} concentration and to a slow elevation of the basal tension in skeletal muscle (Fryer et al., 1989; Lamb and Stephenson, 1990). The slow elevation of basal tension (contracture) elicited by higher concentrations of ryanodine observed in the oesophageal striated muscle preparations from WKY was associated with an elevation of $[Ca^{2+}]_i$, and can be considered to be initiated by Ca^{2+} released from the sarcoplasmic reticulum. The lack of elevation of basal tension in the preparations from SHRSP may be explained by the lower elevation of $[Ca^{2+}]_i$ compared with that in preparations from WKY. A difference in the action of ryanodine on the sarcoplasmic reticulum of striated muscles has been reported between cardiac and skeletal muscles (Sutko et al., 1985). It has been also reported that the effects of ryanodine on the action potential are different in the cardiac muscles of hibernating and non-hibernating chipmunks (Kondo, 1986, 1988). Nevertheless, our data showed that the resting and action potentials were not altered by the drug in oesophageal striated muscle preparations from WKY and SHRSP.

Differences in the action of ryanodine on the release of Ca^{2+} from the sarcoplasmic reticulum may be brought about by one of or a combination of (1) a change in ryanodine concentration around the sarcoplasmic reticulum, (2) a change in sensitivity to ryanodine, (3) a change in the Ca^{2+} release mechanism of the sarcoplasmic reticulum and (4) the amount of Ca^{2+} stored in the sarcoplasmic reticulum, which reflects the amount of Ca^{2+} released. Since ryanodine has been reported to stimulate or to inhibit Ca^{2+} release from the sarcoplasmic reticulum, depending on its concentration (Meissner, 1986), it might be hypothesized that the distinct effects of ryanodine in the oesophageal striated muscle preparations from WKY and SHRSP are attributable to the difference in the intracellular concentration of ryanodine, if any, because of a distinct difference in membrane permeability. The augmentation of the twitch contraction in the presence of ryanodine in the preparations from WKY might be brought about by an increased Ca^{2+} release initiated by the action potential in the presence of a low intracellular concentration of the drug (Meissner, 1986). The depression of the twitch contraction by ryanodine in the preparations from SHRSP might be caused by a decreased Ca^{2+} release in response to a high intracellular concentration of the drug. However, this possibility can be excluded, since the response to ryanodine in SHRSP preparations did not become similar to that in WKY preparations by changing the drug concentration. A high concentration of ryanodine induced an increase in the basal tension associated with an increase in the intracellular Ca^{2+} concentration in WKY but not in SHRSP. These characteristics in WKY and SHRSP oesophageal striated muscles do not correspond to the results reported for extensor digitorum longus muscles, in that although a high concentration of ryanodine elevated the basal tension, it depressed the twitch contraction of the muscles (Fryer et al., 1989).

It has been reported that there is some transition of muscle type in the soleus muscle in SHR, i.e. from slow to fast type (Bachir-Lamrini et al., 1990). In addition, it has recently been reported that this change in muscle type is a cause of sensitivity to caffeine (Bortolotto et al., 2001), which also acts directly on the sarcoplasmic reticulum (Delay et al., 1986; Konishi and Kurihara, 1987). We have

reported that caffeine has a similar effect on the elevation of basal tension and twitch contraction in oesophageal striated muscle, and explain the difference between the preparations from WKY and SHRSP by the change in the sensitivity to caffeine (Sekiguchi et al., 2003). However, a change in sensitivity to ryanodine does not appear to be responsible, since ryanodine produced essentially different responses in WKY and SHRSP preparations. The difference in the resting levels of Ca^{2+} in the sarcoplasmic reticulum is also not responsible for the difference in the effects of ryanodine, since the twitch contraction of both preparations had identical parameters (amplitude of the contraction and rates of contraction and relaxation). Thus, the difference in the effects of ryanodine between WKY and SHRSP cannot to be explained by the changes mentioned above.

It is noteworthy that ryanodine augmented the twitch contraction and elevated the basal tension in the preparations from WKY, while it attenuated the twitch contraction in the preparations from SHRSP without elevating the basal tension. These distinct characteristics may be brought about by a genetic difference in the properties of Ca^{2+} release channels, including the ryanodine receptor, other than changes in sensitivity to the drug.

In conclusion, the effects of ryanodine on oesophageal striated muscle were markedly different between preparations from WKY and SHRSP: the drug augmented the twitch contraction and elevated the basal tension in the former, whereas it attenuated the twitch contraction and had no effect on the basal tension in the latter. It is suggested that the Ca^{2+}-releasing properties, including the ryanodine receptor in the sarcoplasmic reticulum, are genetically altered in the oesophageal striated muscle of SHRSP.

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