Comparison of Endothelium-dependent and -independent Tension Oscillation in Aortae of Stroke-Prone Spontaneously Hypertensive Rats and Wistar Kyoto Rats

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Abstract

Differences in noradrenaline-induced tension oscillations between aortae from stroke-prone spontaneously hypertensive rats (SHRSP) and normotensive control Wistar Kyoto rats (WKY) were studied. Endothelium-intact and -removed ring preparations were made from thoracic aorta of SHRSP and WKY, and isometric contraction was observed. Endothelium-intact preparations from WKY showed tension oscillations in response to high concentration of noradrenaline at significantly higher ratio, while only a few endothelium-removed preparation showed tension oscillations in response to low concentration of the drug. Fifteen out of 41 endothelium-removed preparations from SHRSP showed tension oscillations in response to low concentration of noradrenaline but no preparation showed oscillations in response to high concentration of the drug. Seven and 14 out of 42 endothelium-intact preparations from SHRSP showed oscillatory response to low and high concentration of the drug, respectively. Acetylcholine-induced relaxation and tension oscillations, both of which being significantly less in the preparation from SHRSP. Both the endothelium-independent tension oscillations and endothelium-dependent tension oscillations were abolished by removal of extracellular Ca or by verapamil. It is suggested that aortic smooth muscle of SHRSP possesses the property which produced tension oscillations, while the tension oscillations of WKY aorta is endothelium-dependent. The opening of voltage-dependent Ca++ channel of smooth muscle cell membrane which generates rhythmic contraction is increased in the aorta of SHRSP, while the release of endothelium-derived factors which induces rhythmic activities of smooth muscle cell is decreased.

Key words: tension oscillations, aorta, SHRSP, endothelium, smooth muscle

Introduction

Smooth muscles of small arteries often exhibit tension oscillations in addition to the elevation of basal tension when they are stimulated by agonists or shear stress (Mulvany et al., 1982; Makita et al., 1983; Itoh et al., 1983; Garland, 1987; Katusic et al., 1988). The tension oscillations have been reported to be either endothelium-dependent or -independent. Most of smooth muscles of large artery are usually quiescent under nonstimulated state. In addition,
they do not usually exhibit tension oscillations even when stimulated. Large arterial preparations from hypertensive animals, on the other hand, often exhibit the tension oscillations at rest or in response to stimulation with agonists (Harder et al., 1983; Myers et al., 1985; Lamb et al., 1985; Lamb and Webb, 1989a, b; Bruner et al., 1987; Bruner and Webb, 1988; Bruner and Webb, 1989). This may be brought about mainly by the changes in the smooth muscle cells but changes in the endothelium should also be taken into consideration.

The endothelium-dependent relaxation has been reported to be impaired in the arterial preparations from hypertensive animals (Sunano et al., 1989; Osugi et al., 1990; Luscher and Vanhoutte, 1988). This indicates that the function of endothelium in the initiation of the tension oscillations may also be altered in the preparations from hypertensive animals. Then, the changes would be greater when blood pressure of animals is higher as in endothelium-dependent relaxation (Sunano et al., 1989). Stroke-prone spontaneously hypertensive rats (SHRSP) established by Okamoto et al. (1974) show markedly higher blood pressure than that of control normotensive Wistar Kyoto rats (WKY) and greater changes in endothelium and smooth muscle can be expected. In the present studies, the endothelium-dependent and-independent tension oscillations induced by noradrenaline were examined in SHRSP and WKY aorta.

**Methods**

**Materials**

Male stroke-prone spontaneously hypertensive rats (SHRSP) and control normotensive Wistar Kyoto rats (WKY) of the age of 16 weeks were used. They were originally created by Okamoto et al. (1974) and successively bred in our institute taking great care in the selection of males and females to maintain desired blood pressure of respective animals. These rats were fed with Japanese chow (Funabanhi, SP) and tap water at constant temperature of 25°C and light-dark cycle of 12 hours. Blood pressure of animals was measured by means of a tail cuff method. Prior to the measurement, animals were warmed in a small cage kept at 40°C. Animals were sacrificed by bleeding from the neck under anesthesia with diethyl ether.

**Preparations for mechanical recording**

Thoracic aorta was dissected from animals and connective tissues were removed carefully. Ring preparations of 1 mm width were made from middle portion of the thoracic aorta. In a half of the preparations, endothelium was removed by rubbing luminal surface of the aortic ring with soft rubber. Two tungsten wires of 30 μm diameter were inserted in the lumen of the preparation and each wire was connected to a supporting apparatus and to a force-displacement transducer, respectively. The preparations were incubated in a modified Tyrode's solution of the following composition (mM): NaCl, 137; KCl, 5.4; CaCl₂, 2.0; MgCl₂; 1.0; NaHCO₃, 11.9; NaH₂PO₄, 0.4; glucose, 5.6; Ca (II)–EDTA, 0.027; pH 7.4; equilibrated with a gas mixture of 95% O₂ and 5% CO₂ at 37°C. High-K Tyrode's solution and Ca-free Tyrode's solution were made by replacing NaCl in the solution with equimolar KCl and by removing all CaCl₂ in the solution, respectively.
Experimental design

Changes in tension of the preparations were measured isometrically by a force-displacement transducer (Shin-koh U-gage, Karuizawa). The stretch tension of 800 mg was chosen, since the maximum endothelium-dependent relaxation and twitch-like contractions were observed under this stretch tension, although the maximum contraction of endothelium-removed preparation was observed at the stretch tension of 3,000 mg both in the preparations from WKY and SHRSP. Prior to the experiments, preparations were equilibrated in the modified Tyrode's solution for one hour and, then, subjected to two successive high-K-induced contraction by changing the solution from the modified Tyrode's to high-K Tyrode's solution containing 50 mM K⁺. These procedures were required to obtain constant results in the following experiments.

The tension oscillations and the twitch-like contractions induced by noradrenaline were observed in the concentration-response experiment. The dependency of these contractions on endothelium was observed using endothelium-intact and -removed preparations. The tension oscillations and the twitch-like contractions induced by acetylcholine in endothelium-intact preparation were observed by applying 10⁻⁵ M acetylcholine to the preparation precontracted in the presence of 5×10⁻⁷ M noradrenaline.

Drugs used in the present experiments were: noradrenaline bitartrate (Sigma, St. Louis, USA), acetylcholine chloride (Wako, Osaka, Japan), verapamil hydrochloride (courtesy of Eisai, Japan), N⁶-nitro-L-arginine (L-NNA, Sigma, St. Louis, USA) and N⁶-monomethyl-L-arginine (L-NMMA, Sigma, St. Louis, USA).

Statistical analysis

Obtained values were analyzed by the test for the proportion and P values smaller than 0.05 were considered as statistically significant difference.

Results

Blood pressure of rats

Systolic blood pressure of the rats used in the present experiments (16 week old) was 133±0.9 mmHg (n=20) and 244±3.5 mmHg (n=20), respectively in WKY and SHRSP, being significantly higher in the latter (p<0.001).

Tension oscillations and endothelium

As usual, aortae from WKY and SHRSP exhibited dose-dependent contractile response to noradrenaline (Fig. 1). In endothelium-intact preparation, the threshold concentration of the drug for the initiation of contraction was found to be lower in the preparation from SHRSP when compared with that in WKY aorta. The contraction amplitude increased as the concentration of the drug was elevated in both preparations. In the preparation from WKY, however, noradrenaline of concentrations higher than 10⁻⁶ M caused the decrease in tension. Removal of endothelium enhanced the contractile response to noradrenaline. The threshold concentration for the contraction decreased and contraction amplitude increased in the endothelium-
removed preparation. In the endothelium-removed preparation from WKY, higher concentration of noradrenaline did not cause the decrease in the developed tension.

The endothelium-intact aortic preparations from WKY exhibited apparently phasic response to the each cumulative application of higher concentration of noradrenaline (Fig. 2). In addition, higher concentration of the drug initiated tension oscillations or twitch-like contractions superimposed on the elevated basal tension (Fig. 2 and Table 1). The frequency and the size of the tension oscillations varied among preparations. When endothelium was removed, the tension oscillations or twitch-like contractions were observed in only one out of thirty preparations (Table 1).

Endothelium-removed preparations from SHRSP, on the other hand, exhibited the tension oscillations and/or the twitch-like contractions. They were observed at lower concentrations of the drug (Fig. 2 and Table 1). In some preparations, the twitch-like contractions were observed even in the absence of noradrenaline. However, the tension oscillations were not
Table 1. Occurrence of tension oscillation observed at low and high concentrations of noradrenaline in dose-response experiments.

|        | endothel | n  | low NA (≤10^{-7}M) | high NA (>10^{-7}M) |
|--------|----------|----|-------------------|---------------------|
| WKY    | (+)      | 33 | 0 (0 %)           | 32 (97.0%)          |
|        | (-)      | 30 | 1 (3.3%)          | 1 (3.3%)**          |
| SHRSP  | (+)      | 42 | 7 (16.7%)*        | 14 (33.3%)**        |
|        | (-)      | 41 | 15 (36.6%)**      | 0 (0 %)**          |

Numbers shown in the columns of low NA and high NA indicate the number of preparations which showed the tension oscillation at low and high concentration of noradrenaline, respectively. Ratios of the occurrence are indicated in the parentheses. n, number of preparations which were tested with low and high NA. (+) and (−) in endothel columns indicate aortic ring preparation with or without endothelium, respectively. *, significant difference from WKY preparation (*, p<0.02, **, p<0.001). †, significant difference from endothelium-intact preparation (†, p<0.005, ††, p<0.001).

observed in the presence of higher concentrations of noradrenaline. In endothelium-intact preparations from SHRSP, the tension oscillations could be observed in the presence of both low and high concentration of noradrenaline. The oscillations in high noradrenaline concentrations were observed at markedly lower ratio than WKY (Table 1).

The removal of Ca from incubation medium or the application of verapamil (10^{-5}M) reduced the developed tension and abolished the tension oscillations or the twitch-like contractions of endothelium-intact preparations from WKY. The twitch-like contractions of both endothelium-intact and -removed preparations from SHRSP, which were observed in the absence or presence of noradrenaline, were also blocked by the application of the same concentration of verapamil or by the removal of extracellular Ca (not shown).

When high concentration of noradrenaline was applied non-cumulatively to endothelium-intact preparation from WKY, the preparation responded showing bi- or triphasic contraction. Tension oscillations or twitch-like contractions were usually observed during the course of the contraction (Fig. 3). Removal of endothelium potentiated the contraction as observed by the cumulative application of the drug. Similarly to the observation in cumulative experiment, the tension oscillations or the twitch-like contractions were not observed in endothelium-removed preparation from WKY. Both endothelium-intact and -removed preparations from SHRSP exhibited a monophasic sustained contraction in response to the application of high concentration of noradrenaline as has previously been reported (Osugi et al., 1990) and they exhibited no tension oscillations.

![Fig. 3. Contractions induced by the application of high concentration of noradrenaline (10^{-5}M) in endothelium-intact and -removed preparations from WKY and from SHRSP. Note the differences in the time course of the contraction and in the tension oscillation among four preparations.](image-url)
Tension oscillations observed during endothelium-dependent relaxation

The application of acetylcholine to endothelium-intact preparations, which had been contracted in the presence of noradrenaline, induced dose-dependent relaxation. In the preparation contracted in the presence of $5 \times 10^{-7}$ M noradrenaline, the maximum relaxing response to acetylcholine was observed at the concentration of $10^{-5}$ M both in WKY and SHRSP preparations as has previously been reported (Osugi et al., 1990). The relaxation induced by $10^{-5}$ M acetylcholine was $79 \pm 5.1\%$ (n=9) and $44 \pm 5.0\%$ (n=9) of the tension developed in the presence of $5 \times 10^{-7}$ M noradrenaline, respectively in the preparations from WKY and SHRSP ($p<0.01$).

Fig. 4 shows typical traces of effect of acetylcholine on the endothelium-intact preparations from WKY. As shown in this figure, the application of $10^{-5}$ M acetylcholine to the preparation precontracted in the presence of $5 \times 10^{-7}$ M noradrenaline induced a marked relaxation and initiated tension oscillations (upper) or twitch-like contractions (lower). The size and the frequency of the tension oscillations varied among the preparations and some preparations showed slow-wave-like tension changes of the amplitude close to that of noradrenaline-induced contraction. These tension changes were blocked by the application of verapamil ($10^{-5}$ M). The endothelium-intact preparation from SHRSP exhibited a reduced relaxing response to acetylcholine and only a few preparations showed the tension oscillations.

![Fig. 4. Tension oscillations and twitch-like contractions induced by acetylcholine in the presence of noradrenaline. Both traces were obtained in endothelium-intact preparations from WKY. Acetylcholine ($10^{-5}$ M) was applied to the preparations precontracted in the presence of $5 \times 10^{-7}$ M noradrenaline. Note slow fluctuation of the tension (upper and early phase of lower trace) and twitch-like contractions (late phase of lower trace). Both the tension oscillations and the twitch-like contractions were blocked by the application of verapamil ($10^{-5}$ M).](image)

Table 2. Numbers of the preparations which showed tension oscillation after the application of acetylcholine in endothelium-intact preparations.

| strain | n  | oscillation | twitch |
|--------|----|-------------|--------|
| WKY    | 52 | 46 (88.5%)  | 17 (32.7%) |
| SHRSP  | 55 | 10 (18.2%)**| 5 (9.1%)* |

Numbers shown in the columns of oscillation and twitch indicate number of preparations which showed tension oscillation and twitch-like contractions, respectively. Rates of the occurrence are indicated in the parenthesis. Asterisks indicate significant difference for WKY preparation (*, $p<0.05$, ***, $p<0.001$).
or the twitch-like contractions of low amplitude; the ratio of occurrence of the tension oscillations and twitch-like contractions being significantly lower in the preparation from SHRSP (Table 2).

The acetylcholine-induced relaxation was abolished in the presence of L-NNA (10^{-4} M) or L-NMMA (10^{-3} M). Acetylcholine failed also to induce the tension oscillations in the presence of L-NNA or L-NMMA of the same concentration.

Discussion

Tension oscillations of vascular smooth muscle of hypertensive animals have been reported as spontaneous contraction (Bandick and Sparks, 1970), rhythmic contraction (Holloway and Bohr, 1973), rhythmic activity (De Mey and Boonen, 1988), oscillatory contractions (Lamb et al., 1985; Bruner and Webb, 1988) or oscillatory activity (Mulvany, 1988). In the present experiments, the tension oscillations could be divided into two types; slow tension oscillations and twitch-like contractions.

Although most of reports on the tension oscillations did not state whether the experiments were performed using preparations with or without endothelium, it was revealed in the present experiment that the tension oscillations or the twitch-like contractions of SHRSP aorta could be initiated in the preparation from which endothelium was removed. It can, therefore, be concluded that these tension fluctuation was myogenic in origin. Therefore, the smooth muscle activity to generate contraction rhythmically is somehow enhanced in aorta of hypertensive rats.

A possible explanation for the tension oscillations is the oscillatory release of Ca from sarcoplasmic reticulum as proposed by Makita et al. (1983) in the noradrenaline-induced oscillatory contraction of rabbit mesenteric artery. However, it has also been reported that tension oscillations of the smooth muscles of hypertensive rats were abolished by Ca removal or by Ca antagonist (Lamb et al., 1985; Bandick and Sparks, 1970; Holloway and Bohr, 1973; De Mey and Boonen, 1988). The tension oscillations or the twitch-like contractions of aortic smooth muscle of SHRSP could also be blocked by the removal of extracellular Ca and by the application of verapamil. Similar results have been reported in the smooth muscle of tail artery of SHRSP (Lamb et al., 1985; Bruner and Webb, 1989). Thus, it is suggested that the tension oscillations and twitch-like contractions of the aortic smooth muscle from SHRSP are initiated by Ca influx through voltage-dependent Ca channel. The myogenic tension oscillations were not observed in the aortic smooth muscle of WKY. Then, the oscillatory opening of voltage-dependent Ca channels of SHRSP aortic smooth muscle would be different from those of WKY aorta.

As a cause of the oscillatory changes of Ca influx, noradrenaline-induced rhythmic changes in the membrane potential can be proposed as has been demonstrated in other vascular smooth muscles (Mulvany et al., 1982; Garland, 1977; De Mey and Boonen, 1988; Bolton et al., 1984) Then, the characteristics of membrane electrical activities would be altered in aortic smooth muscle of SHRSP. To support this possibility, Lamb and Webb (1989a, b) reported that the smooth muscle of tail artery of SHRSP exhibited rhythmic regenerative electrical activity in
response to the stimulation with noradrenaline, while no such response was observed in the preparation from WKY. They also observed that these regenerative electrical activities could be blocked by the Ca antagonist (Lamb and Webb, 1989b). Disappearance of the tension oscillations by the application of higher concentration of noradrenaline can be explained by the increased frequency of the regenerative electrical activities which leads to sustained tetanic contraction or by the depolarization blockage of electrical activities (Lamb and Webb, 1989b).

Depression of the tension oscillations or twitch-like contractions of SHRSP aorta by endothelium may be explained by spontaneous (Bullock et al., 1986; Martin et al., 1986; Martin, 1988) or noradrenaline stimulated (Bullock et al., 1986; Cocks and Angus, 1983; Miller et al., 1984; Egileme et al., 1984; Angus et al., 1968) release of endothelium-derived relaxing factor (EDRF). Another possibility is the involvement of endothelium-derived hyperpolarizing factor (Bolton and Clapp, 1986; Huang et al., 1988; Chen et al., 1988). Since the regenerative electrical activity has been reported to be associated with slight depolarization (Lamb and Webb, 1989a, b), the hyperpolarization would depress the electrical activity by repolarizing the membrane.

Smooth muscle of aorta from WKY rarely exhibited the tension oscillations at any concentration of noradrenaline, although the drug induced contraction of similar amplitude to that of smooth muscle of SHRSP aorta. Similar observations have been reported in the tail artery of WKY as described above (Myers et al., 1985; Lamb et al., 1985; Lamb and Webb, 1989a, b; Bruner et al., 1986; Bruner and Webb, 1988; Bruner and Webb, 1989). When endothelium is attached, however, preparations from WKY exhibited the tension oscillations including twitch-like contractions in response to higher concentration of noradrenaline. The endothelium-dependent tension oscillations induced by agonists have been presented in rabbit basilar artery (Garland, 1989), canine basilar artery (Katusic et al., 1988) and in hamster aorta (Jackson, 1988).

The tension oscillations in endothelium-intact preparations are thought to be initiated also by the influx of Ca through voltage-dependent Ca channels, since they were blocked by Ca removal or by the application of verapamil. Then regenerative electrical activities would be involved in the initiation of the tension oscillations. Such an endothelium-dependent regenerative electrical activity has been observed in rabbit basilar artery which was stimulated by noradrenaline (Garland, 1989).

Endothelium-dependent tension oscillations were observed during the acetylcholine-induced relaxation. Since both the incidence of tension oscillations and the relaxation were less in the preparation from SHRSP, the involvement of EDRF in the initiation of tension oscillations is suggested. The possibility is supported by the results that both tension oscillations and relaxation was abolished by L-NNA.

It may then be considered that NO is involved in the oscillatory change in membrane potential. The effect of NO on membrane potential has been reported in the other blood vessels (Tare et al., 1990; Garland and McPherson, 1992; Rand and Garland, 1992; Parkington et al., 1993). NO released by acetylcholine may induce the oscillations of the membrane potential in the presence of noradrenaline.

In summary, in the presence of noradrenaline, the smooth muscle of SHRSP aorta exhibit-
ed tension oscillations or twitch-like contractions, while such activity was rarely observed in the smooth muscle of WKY aorta. Endothelium-dependent tension oscillations, on the other hand, were observed in the aorta from WKY, while only few preparations from SHRSP exhibited such tension oscillations. These tension oscillations would be mediated by the regenerative electrical activities of smooth muscle cell membrane. It is suggested that the characteristics of cell membrane to produce the rhythmic electrical activity is elevated in the smooth muscle of SHRSP, while the release of tension oscillation-inducing factor from endothelium is reduced.

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