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Noxiousness of Hypertension-related Norepinephrine and Upregulation of Norepinephrine Induced by High Intensity Electrical Stimulation in Healthy Volunteers

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Abstract. [Purpose] The purpose of the present study was to assist the design of future experiments on pain therapeutics and to establish the reliability and understanding of animal models of neurotransmitters of sympathetic nerves. [Subjects] The subjects were fifty-five male rats and ten female volunteers. [Methods] In vitro testing of experimental animals, measuring blood pressure, muscle tension, histological changes, intracellular Ca^{2+}, and enzymatic activity. We also induced hypertension-related sympathetic effects by physical therapy with high intensity electrical stimulation as evidenced by 24-hour urine analysis of norepinephrine. [Results] In isometric tension and histological analyse, norepinephrine-induced tension and collagen fibers were significantly increased in muscle strips from hypertensive rat aorta. In $[Ca^{2+}]_i$ analysis, norepinephrine-induced change of $[Ca^{2+}]_i$ in muscle strips from normotensive and hypertensive rat aorta was observed. Analysis by western blotting with anti-phosphorylated antibodies showed that the phosphorylation of ERK1/2 (extracellular signal-regulated protein kinase 1 and 2) and p38 MAPK (p38 mitogen-activated protein kinase) were significantly increased in the norepinephrine-induced state in the rats. Furthermore, high intensity electrical stimulation significantly increased pain-related concentration of norepinephrine in the healthy volunteers. [Conclusion] These results suggest that the application of norepinephrine to aorta muscle strips is associated with changed muscle tension, $[Ca^{2+}]_i$, and phosphorylation of MAPK, and that the increased responsiveness of norepinephrine to high intensity electrical stimulation may be, in part, related to the increase of sympathetic effects.

Key words: Norepinephrine, Electrical stimulation, Sympathetic effects

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INTRODUCTION

Excitation of the sympathetic nervous system is increased by release or activation of norepinephrine in the blood and urine, or increase of active amine, as catecholamine, when pain occurs in an organism[1)]. This is part of the mechanism of the human body to protect itself from noxious stimulus. Homeostasis of the human body, however, may be disturbed, causing a negative result if there is continuous occurrence of noxious stimuli, triggering a vicious cycle[2)]. The rise of sympathetic nervous activity or excitement has been reported to have an intimate connection with the induction and exacerbation of hypertension[3)]. A putative cause of hypertension is excessive salt consumption, which has a direct correlation with this disease, according to the results of studies which used the salt-dependent hypertension animal model and the deoxycorticosterone acetate (DOCA) salt-dependent hypertension model[4)]. When hypertension occurs, the systemic arterial blood flow rate is elevated by reuptake of water and potassium in the distal tubule, which is affected by the renin-angiotensin-aldosterone system responding to excess intake and exposure to chronic stress[4)]. In addition, there is mounting concern in the medical field, because increases in the mortality rate are proportional to the progress from primary to secondary hypertension[5)]. Particularly, increased excitability of the sympathetic nerves is induced by stress factors and the release to transmitters of the sympathetic nervous system of epinephrine and norepinephrine in response to malignant hypertension[3)]. This is now receiving proper medical attention because there is a direct correlation between these factors and hypertension[3)]. Furthermore, the creation and aggravation of hypertension is closely related to the increased peripheral resistance that is caused by elongation of blood vessel wall or other factors, giving rise to change in the blood vessel wall's reaction, and an increase in transmural pressure induced by norepinephrine[4, 6)]. In clinical findings, myotonic and structural changes of the blood vessel wall, especially, are

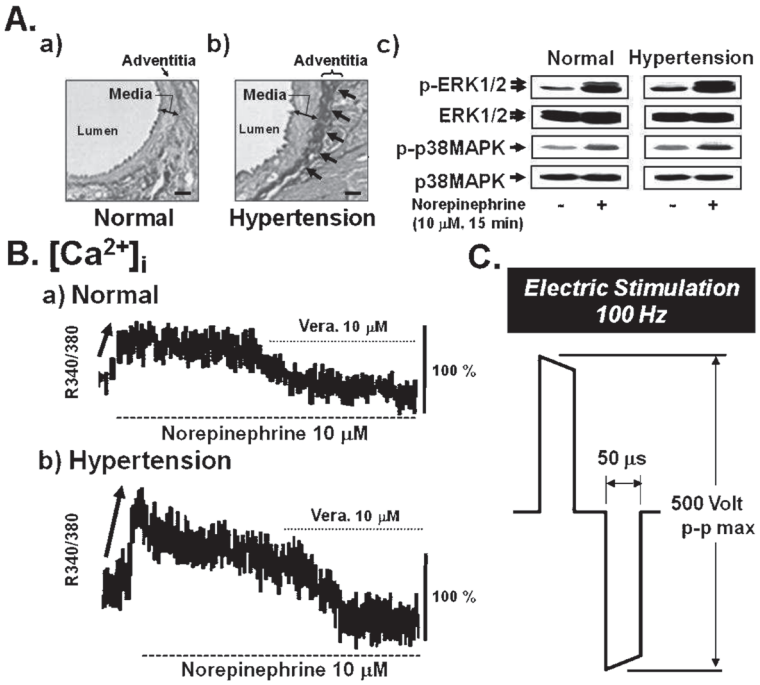

Fig. 1. Representative light micrographs of blood vessel, MAPK activity, and intracellular Ca^{2+} in normotensive and DOCA-salt hypertensive rats. Histological changes (A-a, A-b), phosphorylation of ERK1/2 and p38 MAPK (A-c). Changes in intracellular Ca2+ (B) were measured in rat blood vessel and gastrocnemius tissues. Histological changes were analyzed in muscle strips using Verhoeff's staining. The expression and the phosphorylation of ERK1/2 and p38 MAPK were examined using specific antibodies. The intracellular Ca2+ was measured using acetoxymethyl ester of fura-PE3 as a fluorescent dye which was excited with ultraviolet light. Bars = 25 ?m. ERK1/2, extracellular signal-regulated protein kinase 1 and 2; p38MAPK, p38 mitogen-activated protein kinase; Vera, L-type Ca2+ channel inhibitor; [Ca2+]i, intracellular Ca2+; R340/380, wavelengths 340 and 380 nm of ultraviolet.

directly connected with cardiovascular disorders such as hypertension, cerebral hemorrhage and angina[4, 7]. Excessive tension of the vascular smooth muscle is induced by hyperactivation of the sympathetic nerves, and phosphorylation of mitogen-activated protein kinases (MAPKs), and remodeling of cells takes place to balance the pathogenic metamorphosis of hypertension[4, 8, 9]. Previous studies have reported that the controlled release of transmitters and excitement of the sympathetic nerves (using interventions such as stimulus by electronic needle and therapeutic massage to decrease blood pressure) do alleviate pain, and restrain the activity of sympathetic nerves[10, 11]. However, it has been noted that these interventions can give rise to a contrary result, if the intervention method is flawed. For example, the induction of muscle cramps or pain that occurs due to an inappropriate treatment program using electric stimulus can actually lead to negative results by inappropriate increase of the sympathetic nervous activation[12, 13]. A previous study focused on inducing fluctuation of hormones without any muscle cramp using an electronic stimulus device[14]. However, previous studies may have been inclined to overlook. Consequently, in the present study, we investigated the effect of fluctuation of a relatively high intensity of electrical stimulation on the pain intensity and sympathetic activity caused by severe muscle contractions in volunteers, with the dual objectives of assisting the design of future experiments on pain therapeutics, and establishing the reliability and understanding of animal models of neurotransmitters of sympathetic nerves.

SUBJECTS AND METHOD

Fifty-five male Sprague-Dawley rats (190–200 g; Daehan Biolink, Korea) were used in this study. The rats were separated into groups of normotensive and DOCA-salt hypertensive rats. The latter group were uninephrectomized and after one week received a subcutaneous silicon rubber implant impregnated with DOCA (200 mg/kg) under intramuscular anesthesia (3.5 mg/kg xylazine hydrochloride and 100 mg/kg ketamine hydrochloride)[4]. The DOCA-salt hypertensive rats received 0.9% NaCl plus 0.1% KCl

drinking water solution. The left common carotid artery was cannulated and connected to a physiological pressure transducer (P23XL, Viggo-Spectramed, USA) which measured systolic and diastolic blood pressures. We enucleated blood vessels from experimental rats and fixed them in 4% buffered formalin. Paraffin blocks were made after 24 hours. The samples were then incubated on glass slides at 60 °C for 30 minutes after being cut longitudinally into 3 μm-thick sections. Verhoeff staining was conducted to stain collagen fibers[15]. We also measured isometric tension to observe the effect of sympathetic neurotransmitters on vascular tissue[9]. Muscle tension was recorded isometrically between a force-displacement transducer (FT 03, Grass, USA) and a physiograph (7WC, Grass, USA). Furthermore, intracellular Ca^{2+} in cells was measured, as in a previous study[16], using acetoxy-methyl ester of fura-PE3 as a fluorescent dye. The specimens were illuminated with two wavelengths of ultraviolet light, 340 and 380 nm, alternating at a frequency of 48 Hz. The ratio of the emission fluorescence (R340/380) in a rectangular window of a particular size was measured through a barrier filter of 500 nm, using a microphotoluminescence measurement system (CAF110, JASCO, Japan)[16]. The expression and activity of MAPK were measured in rat aortic smooth muscle using Western blot analysis with anti- and anti-phosphorylated MAPK antibodies[17]. Random urine samples were also collected from ten female volunteers who did not have any physical or psychiatric disease and who were not in their menstrual period (age: 21–29 yrs; BW: 53 ± 6.7 kg; height: 161 ± 5.2 cm). Subjects were separated into two groups. The experimental group received electric stimulus and the other (control group) did not. This experiment used a simulator (Dynaroshiftor DS-3004, Asahi Denshi Co., Japan). The electric stimulus was adjustable from 50 to 190 μsec, and we applied 100 Hz electric stimulation for 15 minutes using a current of pulse-to-pulse amplitude 500 V (Fig. 1C). Electric stimuli were applied to subjects while they were in a supine position using 8 probes, which were attached to meridian points (CV-3, CV-4, Ki-12, SP-6, LR-3). Electric stimulus was applied to the subjects until a visible muscle contraction was observed without intolerable pain. For evaluation of pain after electronic intervention, the Visual Analogue Scale (VAS), Faces Pain Rating Scale (FRS) and Iowa Pain Thermometer (IPT) were used. We adopted the mean values of three repeated measures to compensate for the defects of these subjective assessments[18]. Analysis of norepinephrine and epinephrine in 24-hour urine was performed using a High Performance Liquid Chromatography-Regent set (Bio-Rad Laboratories, USA). The protocol for the study was approved by the Committee of Ethics in Research of the University of Yongin, in accordance with the terms of Resolution 5–1-20, December 2006. Statistical analyses were conducted using Prism for Windows, version 4.0. The data are expressed as mean ± SEM. Differences between parameters were analyzed using Student's t test for comparisons of groups and by analysis of variance (ANOVA) for multiple comparisons. A p value of <0.05 was considered statistically significant.

RESULTS

Systolic (SBP) and diastolic blood pressure (DBP) were measured by direct hemodynamometry of the normotensive and hypertensive groups and evaluated after the experimental operation. There was a significant difference between the groups in SBP and DBP at 4–5 weeks in the post-operative period (Table 1). The hypertensive group showed more significant increases than the normotensive group in weights of the adrenal gland and aorta, and thickness of media (Table 1). Proliferation of collagen fiber in adventitia in the hypertensive group was histologically observed, and is shown in red (arrow) in Fig. 1A-a and 1A-b. In isometric tension, the hypertensive group showed more significant increases than in normotensive group in the reaction of norepinephrine in the vascular tissue of rats (Table 2). In analyse of ERK1/2 and p38MAPK activities and intracellular Ca^{2+}, both the hypertensive group and normotensive group demonstrated significant increases in the norepinephrine-induced sympathetic condition (Table 2, Fig. 1A-c, 1B). In the results of the high frequency intense electric stimulus for 15 minutes, the pain of the experimental group showed a more significant rise than that of the control group after electric intervention (Table 3). Change of norepinephrine and epinephrine also increased more in the experimental group than in the control group after high intensity electric intervention (Table 3).

DISCUSSION

Negative noxious stimuli can create a vicious cycle, which is repeated when the threshold of the reaction exceeds the stress intensity of the entity[3]. This is especially true in the case of forceful hyperplasia or the action of catecholamine which is known to have an adverse effect on the mechanism pain induction, especially in hypertension, because it is likely to aggravate the excessive tension in the vascular smooth muscle cells that occurs in this disease[3, 19]. Studies by Dahl and others have reported that the salt-dependent hypertension and the DOCA-salt hypertension animal models are important models for experiments in hypertension research[4, 6, 20]. There is a direct correlation between the secondary hypertension of Korean adults and the DOCA-salt hypertension animal model. Therefore, in this study, we confirmed the differences and character by observation and comparison. Hypertensive rats showed not only more hypertrophy of vascular tissue and the adrenal gland, but also increasing thickness of media, compared to the normotensive rats. A number of studies have corroborated the results of our present study[6, 7]. Growth of vascular wall thickness was verified as a coincident tendency in the primary hypertension animal model, and this result is considered to be highly significant[21]. DOCA-salt is an important factor inducing or aggravating hypertension. Previous studies have reported remarkable increases in the vascular wall thickness and the manifestation of endothelin-1 when DOCA-salt is administered to spontaneous hypertensive rats (SHR)[22]. In the present study, we confirmed significant growth of collagen fibers with proliferation in the vascular adventitia. This outcome is not only similar those reported in previous

Table 1. The changes in blood pressure, adrenal gland, aorta, and the thickness of media of normotensive and DOCA-salt hypertensive rats

	Systolic Blood Pressure (mmHg)					
	0 wk	1 wk	2 wk	3 wk	4 wk	5 wk
Normal	89.5 ± 4.5	98.0 ± 12.0	110.0 ± 15.3	120.0 ± 20.0	140.0 ± 12.2	126.3 ± 9.0
Hypertension	109.3 ± 4.7	125.0 ± 16.1	141.7 ± 18.3	162.5 ± 22.5	182.5 ± 12.3*	166.3 ± 5.5*
	Diastolic Blood Pressure (mmHg)					
	0 wk	1 wk	2 wk	3 wk	4 wk	5 wk
Normal	88.0 ± 3.6	90.0 ± 5.0	91.7 ± 1.7	93.0 ± 6.0	96.1 ± 3.0	103.3 ± 2.3
Hypertension	110.3 ± 5.2	110.0 ± 5.0	113.3 ± 1.7	114.0 ± 7.0	119.0 ± 2.6	127.6 ± 2.2*
	Adrenal Gland (g)		Aorta (g)		Thickness of Media (%)	
Normal	0.04 ± 0.02		36.0 ± 3.6		100.0 ± 0.00	
Hypertension	0.11 ± 0.02*		61.3 ± 5.8*		152.5 ± 18.0*	

* $p<0.05$

Table 2. The relationship of isometric tension and MAPK-activity on the norepinephrine-induced response in muscle strips

	Isometric tension with NE 10μM (%)	p-ERK1/2 (%)		p-p38MAPK (%)	
		Control	NE (10μM)	Control	NE (10μM)
Normal	123.8 ± 9.6	100.0 ± 0.0	223.0 ± 26.0†	100.0 ± 0.0	172.3 ± 23.2†
Hypertension	199.3 ± 26.5*	150.3 ± 16.5*	263.0 ± 58.6†	143.3 ± 20.3*	232.3 ± 37.5†

ERK1/2, extracellular signal-regulated protein kinase 1 and 2; p38 MAPK, p38 mitogen-activated protein kinase; NE, norepinephrine. *,† $p<0.05$

Table 3. The effects of high intensity electrical stimulation on pain and on urine epinephrine and norepinephrine of healthy volunteers

	VAS (score)	FRS (score)	IPT (score)	Norepinephrine (μg/day)	Epinephrine (μg/day)
Control	2.0 ± 0.6	1.7 ± 0.7	2.0 ± 1.0	42.1 ± 1.8	13.9 ± 1.0
Electrical Stimulation	6.7 ± 1.5*	5.3 ± 1.5*	6.3 ± 1.8*	75.5 ± 5.4*	21.1 ± 2.6*

VAS, visual analogue scale; FRS, faces pain rating scale; IPT, Iowa pain thermometer. * $p<0.05$.

studies, but also confirms the morbid change of vascular tissue, such as stiffening of the arterial tissue during the contraction of hypertension[15]. MAPK is a factor involved in morbid alteration, such as excessive tension of blood vessels, lesioning in endothelial cells, and stiffening of vascular tissue during the contraction of hypertension[4]. Furthermore, the significance of MAPK in hypertension has been noted in prior studies which found that vascular remodeling, and injury of adrenal tissue are modulated by the administration of anti-MAPK[23]. The existence, biological activity, and active mechanisms of MAPK first became known through experiments with *saccharomyces cerevisiae*[24]. It has since become recognized as playing a key role in the promotion of cellular mitosis, growth, apoptosis, control of the cellular life cycle, and induction of muscular contraction, and the inflammatory reaction[4, 24]. In addition, the activity of MAPK has been emphasized more in therapeutic pain studies than other areas, because it has been reported that MAPK participates in the route of communication of pain signals as a crucial signal transduction messenger in the reaction of muscular contraction to noxious stimulus[25]. On the other hand, increasing vascular tension and peripheral resistance induced by lifestyle and environmental stress factors, such as physical or chemical stimulus and heavy workload, are significant factors in the induction of hypertension. This is chiefly true for the rise of the activation and release of catecholamines which cause an increase in peripheral resistance. Thus, a number of studies have reported that rising vascular tension plays an important role in the induction or aggravation of hypertension[3, 19]. There are significant differences in the release times of norepinephrine and epinephrine. Despite this, they have been accepted as indicators of sympathetic nervous system activity, which is increased by their release into or action the blood and urine in response to noxious stimulus[26]. Therefore, we applied norepinephrine to vascular tissue of normotensive and hypertensive rat

models. A change in muscular tension and activation of MAPK was observed. The rats with hypertension showed more significant increases than normal rats in muscular contraction, similar to the findings of a previous study[6]. The results of other studies have reported conflicting outcomes, case by case, which were contingent on tissue. There are reports that sensitivity of hyperpietic vascular tissue is not significantly influenced by norepinephrine in normal rats[27]. However, in the present study, the norepinephrine-related sensitivity of the hypertension group was much higher than that of the normotensive group as the hypertensive group showed significantly higher rises than the normotensive group in muscular tension and activation of MAPK. These results also provide evidence that chronic tension and stress are likely to be important factors in the induction or aggravation of hypertension, and we emphasize the significance of MAPK in playing a key role in the norepinephrine-induced contraction mechanism. The significance of MAPK in hypertension has been noted in previous studies, which have reported that there is a direct correlation between muscular tension or alteration in levels of active MAPK and application of norepinephrine[28]. However, norepinephrine-induced tension and alteration of MAPK activity in DOCA-dependent hypertensive rats compared with normotensive animals has suffered from an inauthentic condition. Therefore, in the present study, we performed an experiment that confirmed the correlation of MAPK with norepinephrine in the vascular tissue between normotensive and hypertensive rats using a MAPK antibodies. The increases of norepinephrine-induced contraction and alteration of MAPK activity were restrained by MAPK antibodies. These results confirm the increase of contraction is induced by norepinephrine in direct correlation with the rise of MAPK activity. Some previous studies have attempted to use these experimental findings in therapeutic intervention methods using acupuncture, electroacupuncture, and low-frequency electric stimulus[29, 30]. Other studies have also reported that intraocular pressure, blood pressure, norepinephrine, and dopamine were decreased by electroacupuncture stimulus the sciatic nerve region of rabbits, 1–3 hours later[31]. The levels of blood pressure and epinephrine or norepinephrine in the blood that increase the blood pressure level under immobilization stress in rats were alleviated after rats were given electroacupuncture stimulus on acupuncture points HT3 and PC6[32]. Periodontal norepinephrine, dopamine, corticosterone, and ACTH, which increases the blood pressure under electric stimulus in rats, were also decreased by electroacupuncture stimulus to an acupuncture point (LI4) for 15 minutes[33]; however, high intensity electrical stimulation is likely to have severe side-effects[12, 13]. Our results that the increasing pain, which was caused by high intensity electrical stimulation, is closely correlated with the activation of norepinephrine and epinephrine. Therefore, health care experts such as physiotherapists and massage therapists should remember that all therapeutic interventions should focus on specific manners that improve the subjective sensations of the patient. To avoid unnecessary muscular contractions or pain during treatment for dolorific control is of high importance. However, the present results cannot be used to design as an intervention, because more multidimensional investigations are needed.

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