INHIBITION OF ADRENERGIC TRANSMISSION BY METHIONINE- AND LEUCINE-ENKEPHALINS IS IMPAIRED IN THE MESENTERIC VASCULATURES OF SPONTANEOUSLY HYPERTENSIVE RATS

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The present study was carried out to investigate the effects of enkephalins (methionine-enkephalin: Met-Enk, leucine-enkephalin: Leu-Enk) on the adrenergic neurotransmission in hypertension. Perfused mesenteric vasculatures were prepared in spontaneously hypertensive rats (SHR, Okamoto and Aoki strain, 7–10 weeks old) and age-matched Wistar Kyoto rats (WKY), and the effects of these peptides on vascular responsiveness as well as norepinephrine release from the sympathetic nerve endings were examined. Pressor responses to electrical nerve stimulation were inhibited in a dose-dependent manner by Met-Enk and Leu-Enk, and the inhibition was antagonized by naloxone. Norepinephrine release during electrical nerve stimulation was also suppressed by these peptides. In SHR, stimulation-evoked pressor responses and norepinephrine release were significantly enhanced compared to those in WKY, while the suppressive magnitudes of the responses by Met-Enk and Leu-Enk were smaller in SHR than in WKY.

These results demonstrate that Met-Enk and Leu-Enk affected presynaptic sites of blood vessels and caused a decrease in electrically-stimulated norepinephrine release from the sympathetic nerve endings. The lower reduction in norepinephrine release and vascular responsiveness by Met-Enk and Leu-Enk in SHR suggests an insufficient regulation of the vascular adrenergic neurotransmission by the opioid peptides in this model of hypertension.

MANY neurally localized peptides are known to exist not only in the central nervous system, but also in kidneys, heart, adrenal medulla and peripheral blood vessels. These peptides are also thought to be involved in the cardiovascular regulation,^{1–3} especially the opioid peptides, such as methionine-enkephalin and leucine-enkephalin. They are proposed to act as co-transmitters to the catecholamines in

post-ganglionic nerve fibers, suggesting a possible role in the modulation of vascular resistance!^{1–5}

Recently, important changes have been described in the opioid system in several models of hypertension. Gaida et al⁶ reported that the content of adrenal gland leucine-enkephalin was lower in spontaneously hypertensive rats-stroke prone strain (SHR-SP) than that in normotensive controls, while β -endorphin in the neuro-intermediate lobe of the pituitary was higher in SHR-SP. Zamir et al⁷ observed that hypertensive-Sabra rats had higher levels of endogenous opioid peptides in their cervical spinal cord, hypothalamus, and pituitary gland as compared with levels in their normotensive controls. Further,

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Farsang and Kunos⁸ found that naloxone, an opioid receptor antagonist, reserved the blood pressure reduction induced by clonidine in hypertensive rats. Thus, it is strongly suggested that altered opioid activities could be a factor in the pathogenesis of hypertension. The purpose of the present study was to investigate the role of opioid peptides in adrenergic neurotransmission in hypertensive blood vessels.

MATERIALS AND METHODS

Male normotensive Wistar rats (WRs), weighing 250–350 g ($n = 23$) were used for the preliminary studies of the effects of opioid peptides in blood vessels. Male spontaneously hypertensive rats (SHR, Okamoto and Aoki strain, 7–10 weeks of ages) were examined in comparison with age-matched Wistar Kyoto rats (WKY). The systolic blood pressure, measured by the tail-cuff method (programmed electro-sphygmomanometer, Narco Biosystem Inc., Model PE-300), was 167.3 ± 2.9 mmHg (mean $\pm$ SEM, $n = 10$) in SHR, and 133.2 ± 2.1 mmHg ($n = 10$) in WKY.

Rats were anesthetized with pentobarbital (40 mg/kg, intraperitoneal injection), and perfused mesenteric vasculatures were prepared according to the method of Castellucci et al.⁹ The superior mesenteric artery was perfused through a cannula inserted at its origin from aorta. In each preparation, only four branches from the superior mesenteric artery trunk were used. All other branches were tied off. The isolated preparation was placed in a chamber maintained at 37°C and gently laid on gauze to avoid any traction on the cannulated artery. The preparation was perfused with the modified Ringer-Locke solution (mmol/l: NaCl 120.7, KCl 5.9, CaCl₂ 2.5, MgSO₄ 1.3, NaHCO₃ 15.5, NaH₂PO₄ 1.2 and glucose 11.5, pH 7.4, 37°C), bubbled with 95% O₂ and 5% CO₂ mixture. A constant flow rate was maintained with a peristaltic pump (Harvard apparatus, Model 1200) at 0.8 ml/min. Changes in the perfusion pressure were monitored with a pressure transducer connected to a polygraph (Nihon Kohden, Model CP-620 G).

Periarterial nerve stimulation was performed with bipolar platinum electrodes around the proximal end of the mesenteric artery. The stimulation was applied at a supramaximal voltage (40 V), with rectangular pulses of 5 msec duration for 1 min at 5 and 15 Hz (electrical stimulator: Nihon Kohden, Model SEN-3201). Pressor responses to the electrical nerve stimu-

lation were determined as increases in the perfusion pressure. After perfusion of the mesenteric vascular beds was initiated, the basal perfusion pressure was allowed to stabilize for 30 min prior to onset of the experimental procedure.

Measurement of norepinephrine release during electrical nerve stimulation in the mesenteric vasculatures

To measure norepinephrine release from sympathetic nerve endings, the perfusate through the mesenteric preparation was collected in a tube, containing EGTA (90 mg/ml) and glutathione (60 mg/ml) in the ratio of 20 μ l/ml of the perfusate. The collecting periods were 3 min before the nerve stimulation (A) and 2 min after cessation of 1 min-stimulation (total 3 min) (B). The norepinephrine release evoked by the electrical nerve stimulation was defined as the norepinephrine overflow, which was the difference of the norepinephrine contents between (A) and (B), and was normalized as nanograms per gram of wet tissue weight for each preparation.

Norepinephrine in the perfusate was adsorbed on alumina, extracted in 200 μ l of perchloric acid (0.1 mol/L), and assayed by the high performance liquid chromatography (HPLC)^{10,11} with an electrochemical detector (Bioanalytical system, Model LC-4A, carbon electrode, 700 mV). The HPLC unit was equipped with a delivery system (Waters Assoc., Model 510, flow rate 1.0 ml/min), an automatic injector (Waters Assoc., Model 710B, injected volume 100 μ l) and Biophase ODS 5 μ m column. The solvent for the separation of norepinephrine was 0.1 mol/L of monochloroacetic acid with 2 mmol/L of EDTA, 300 mg/L of sodium octyl sulfate and 9% (v/v) of acetonitrile (pH 3.02 at room temperature).

In the first series of experiments, the pressor responses and norepinephrine release during electrical nerve stimulation were examined in the presence of methionine-enkephalin (Met-Enk) or leucine-enkephalin (Leu-Enk) in normotensive WRs. Effects of these peptides on exogenously applied norepinephrine (3.3 μ g of 1-norepinephrine in 0.1 ml of buffer, bolus injection) were also evaluated. Then, the effects of Met-Enk and Leu-Enk were compared between SHR and WKY. Met-Enk and Leu-Enk were added to the perfusion medium to achieve final concentration of 1.0×10^{-7} M to 5.0×10^{-6} M. After the drug administration, a 9 min-period elapsed before the next electrical stimulation or exoge-

TABLE I EFFECTS OF METHIONINE-ENKEPHALIN (MET-ENK) AND LEUCINE-ENKEPHALIN (LEU-ENK) ON PRESSOR RESPONSES AND NOREPINEPHRINE (NE) OVERFLOW DURING ELECTRICAL NERVE STIMULATION (15 Hz, 40 V, 1 MIN) IN ISOLATED MESENTERIC VASCULATURES OF NORMOTENSIVE WISTAR RATS

Concentration		Pressor Responses	NE Overflow
Met-Enk (n = 4)	$1.0 \times 10^{-7} M$	$57.2 \pm 7.6\%^*$	$58.8 \pm 3.3\%^*$
	$5.0 \times 10^{-7} M$	$56.7 \pm 3.3\%^*$	$48.3 \pm 1.7\%^*$
	$1.0 \times 10^{-6} M$	$22.9 \pm 4.3\%^*$	$33.3 \pm 2.9\%^*$
Leu-Enk (n = 4)	$1.0 \times 10^{-7} M$	$66.2 \pm 3.9\%^*$	$77.8 \pm 2.7\%^*$
	$5.0 \times 10^{-7} M$	$53.1 \pm 0.9\%^*$	$58.6 \pm 4.8\%^*$
	$1.0 \times 10^{-6} M$	$26.5 \pm 6.0\%^*$	$43.1 \pm 5.6\%^*$
	$5.0 \times 10^{-6} M$	$24.1 \pm 7.5\%^*$	$38.8 \pm 2.6\%^*$

Values are expressed as percentage ratios of the corresponding control values in the absence of the peptides (mean $\pm$ SEM, $^*p < 0.05$).

Fig.1. Typical example of naloxone effect on Met-Enk-induced inhibition of pressor responses in rat mesenteric vasculatures.

nous norepinephrine application. For each preparation, the results were evaluated by comparing the responses before (control) and during the infusion of the peptides (experimental), and then expressed as percentage ratios of the control response for each experiment. Thus, a value greater than 100% would indicate enhancement and that less than 100% would represent inhibition.¹²

Values are expressed as means $\pm$ SEM. Statistical significances were determined by Student's t-test or Mann-Whitney U-test. The differences of $p < 0.05$ were considered significant.

Met-Enk, Leu-Enk, naloxone and 1-norepinephrine were purchased from Sigma Chemical Co., Ltd. (USA).

RESULTS

1. Effects of methionine-enkephalin (Met-Enk) and leucine-enkephalin (Leu-Enk) on pressor responses and norepinephrine overflow in the mesenteric vasculatures of normotensive Wistar rats (WRs)

Pressor responses and norepinephrine overflow during electrical nerve stimulation were

TABLE II PRESSOR RESPONSES AND NOREPINEPHRINE (NE) OVERFLOW DURING ELECTRICAL NERVE STIMULATION IN THE PERFUSED MESENTERIC VASCULATURES OF SHR AND WKY

(Pressor responses)		5 Hz	15 Hz
SHR	(n = 10)	20.5 ± 3.6 mmHg*	73.6 ± 3.1 mmHg*
WKY	(n = 10)	7.2 ± 1.0 mmHg	41.6 ± 2.8 mmHg
(NE overflow)		5 Hz	15 Hz
SHR	(n = 10)	0.63 ± 0.05 ng/g*	2.03 ± 0.09 ng/g*
WKY	(n = 10)	0.26 ± 0.03 ng/g	1.01 ± 0.04 ng/g

Electrical nerve stimulation was performed at 5 and 15 Hz frequencies (40 V, 5 msec duration of rectangular pulses for 1 min). Pressor responses are represented as increases in the perfusion pressure of the preparations. Norepinephrine overflow is expressed as nanogram/gram of wet tissue weight of each preparation (mean ± SEM, *p < 0.05, statistical significance between SHR and WKY).

TABLE III EFFECTS OF METHIONINE-ENKEPHALIN (MET-ENK) AND LEUCINE-ENKEPHALIN (LEU-ENK) ON STIMULATION-EVOKED PRESSOR RESPONSES AND NOREPINEPHRINE (NE) OVERFLOW DURING ELECTRICAL NERVE STIMULATION (15 Hz) IN THE MESENTERIC VASCULATURES OF SHR AND A COHORT OF WKY RATS

Met-Enk		1.0 × 10 ⁻⁷ M	5.0 × 10 ⁻⁷ M	1.0 × 10 ⁻⁶ M
(Pressor responses)				
SHR	(n = 5)	99.6 ± 8.6%*	85.2 ± 11.5%*	77.7 ± 8.1%*
WKY	(n = 5)	53.5 ± 3.6%*	34.5 ± 2.5%	29.5 ± 2.4%
(NE overflow)				
SHR	(n = 5)	92.6 ± 6.8%*	77.6 ± 4.9%*	72.0 ± 5.8%*
WKY	(n = 5)	55.2 ± 3.1%	52.4 ± 2.7%*	36.7 ± 2.0%
Leu-Enk		1.0 × 10 ⁻⁷ M	5.0 × 10 ⁻⁷ M	1.0 × 10 ⁻⁶ M
(Pressor responses)				
SHR	(n = 5)	76.2 ± 5.5%*	73.7 ± 0.6%*	57.8 ± 2.5%*
WKY	(n = 5)	56.1 ± 2.8%	47.5 ± 3.9%	27.9 ± 5.3%
(NE overflow)				
SHR	(n = 5)	80.0 ± 1.5%	69.6 ± 3.7%	57.5 ± 4.6%
WKY	(n = 5)	64.6 ± 3.7%	46.2 ± 3.6%	33.5 ± 2.5%

Values are expressed as percentage ratios of the corresponding control values in the absence of the peptides in SHR and WKY, respectively (mean ± SEM, *p < 0.05 between SHR and WKY determined by Mann-Whitney U-test).

51.3 ± 2.4 mmHg (n = 15) and 1.08 ± 0.09 ng/g of wet tissue weight (n = 15), respectively. Table I shows the effects of Met-Enk and Leu-Enk on pressor responses to electrical nerve stimulation. Met-Enk and Leu-Enk inhibited the stimulation-evoked pressor responses in a dose-dependent manner. Stimulation-evoked norepinephrine overflow from the vascular adrenergic neurons was also suppressed by these peptides (Table I).

In the presence of naloxone (a potent antagonist for opioid receptors), the inhibitory effects of Met-Enk on pressor responses (Fig. 1) and norepinephrine overflow were diminished (15 Hz: pressor responses, Met-Enk 5.0 × 10⁻⁷ M with naloxone 4.0 × 10⁻⁶ M, 99.5 ± 10.3%, NE overflow, 91.0 ± 6.5%, n = 4). Similarly, naloxone antagonized the effects of Leu-Enk on stimulation-evoked pressor responses and norepinephrine overflow (15 Hz: pressor responses,

Leu-Enk 5.0×10^{-7} M with naloxone 4.0×10^{-6} M, $88.7 \pm 9.2\%$, NE overflow $89.5 \pm 7.8\%$, $n = 3$).

Vasoconstrictor responses to exogenous norepinephrine were not strongly affected by Met-Enk and Leu-Enk ($3.3 \mu\text{g}$ of NE application, Met-Enk 1.0×10^{-6} M, $76.2 \pm 18.4\%$, $n = 4$; Leu-Enk 1.0×10^{-6} M, $71.3 \pm 9.2\%$, $n = 4$; control responses without the peptides, 55.0 ± 4.2 mmHg, $n = 8$).

2. Effects of Met-Enk and Leu-Enk on the pressor responses and norepinephrine overflow in the mesenteric vasculatures of SHR and WKY

There were no significant differences between SHR and WKY on resting perfusion pressure of the preparations and spontaneous norepinephrine outflow into the perfusate during the unstimulated period (basal perfusion pressure: SHR 22.5 ± 2.5 mmHg, $n = 10$, WKY 21.0 ± 1.6 mmHg, $n = 10$; spontaneous NE overflow: SHR 0.29 ± 0.04 ng/g of wet tissue weight, $n = 10$, WKY 0.28 ± 0.04 ng/g of wet tissue weight, $n = 10$).

Table II shows the pressor responses and norepinephrine overflow during electrical nerve stimulation in SHR and WKY. These responses were significantly greater in SHR than in WKY. Alternatively, as shown in Table III the suppressive magnitudes of these responses by Met-Enk and Leu-Enk were attenuated in SHR compared with WKY.

DISCUSSION

Our experiments demonstrated that Met-Enk and Leu-Enk decreased the stimulation-evoked norepinephrine overflow from the adrenergic neurons in rat mesenteric vasculature in a dose-dependent manner. This result is consistent with previous reports that opioid peptides showed an inhibition of norepinephrine release in rabbit ear artery^{13,14} and in other tissues.¹⁵⁻¹⁷ Additionally, the inhibition of norepinephrine overflow was associated with a concomitant reduction of pressor response to electrical nerve stimulation. In contrast, the vasoconstrictor responses to exogenously applied norepinephrine were not significantly affected by Met-Enk and Leu-Enk. Thus, these peptides might cause vasodilation by affecting presynaptic adrenergic nerve terminals in rat mesenteric vasculatures. Further, the suppression of pressor responses and norepi-

nephine overflow by Met-Enk and Leu-Enk was antagonized by naloxone, which may suggest that specific opioid receptors were present on the nerve terminals in the mesenteric vasculatures. The opioid system is especially complex because of the multiple species of opioid peptides and multiple forms of receptor subtypes.¹⁸ Illes et al reported that only substances with pronounced activity at delta and/or kappa receptors were potent agonists in the rabbit ear artery, and proposed that the noradrenergic fibers innervating the rabbit ear artery did not possess presynaptic mu-receptors, but do possess delta- or kappa-receptors.¹⁴ Most potent selective delta-agonists are Met-Enk and Leu-Enk.^{14,19,20} Thus, it seems likely that the release-inhibiting opioid receptors might be delta-type in rat mesenteric vasculature. However, the possible involvement of other types of opioid receptors cannot be excluded.

In the study of SHR, stimulation-evoked pressor responses and norepinephrine overflow were significantly greater than those in WKY; alternatively the degree of these responses by Met-Enk and Leu-Enk was less in SHR than in WKY. These results may suggest the insufficient regulation of vascular adrenergic transmission by enkephalins in SHR.

Recently, it has been strongly proposed that opioid-system may play a role in the pathogenesis of hypertension.⁶⁻⁸ The alterations in opiate contents, receptor binding in the nervous cells or plasma concentrations have been reported in hypertension.^{6,7,21,22} Consistent with these previous reports, Zamir et al observed a reduced sensitivity to pain in rats and humans with genetic hypertension^{7,23,24} although the relationship of the change of pain perception to the pathogenesis of hypertension is not well known. Studies with administration of opioid peptides in vivo have shown that SHR differed from normotensive control rats in their responses to the peptides.^{25,26} As for the interactions with the sympathetic nerve system, opioid peptides are thought to be endogenous sympatho-depressors both in central and peripheral nervous systems. Kraft et al have reported that plasma concentrations of β -endorphin and Met-Enk were lower in patients with essential hypertension than in normotensive controls. In contrast, they noted that the plasma norepinephrine concentration was higher in hypertensives, and proposed that reduced opioidergic activity might induce the increased sympathetic nerve activity in these

patients²² It has been also observed that treatment of hypertensive patients with clonidine induced a significant increase in plasma β -endorphin, but not in normotensives²¹ These results may suggest that release of peptide hormones is not sufficient to prevent an increase in arterial blood pressure. In this study, we demonstrated that inhibitory neurovascular effects of Met-Enk and Leu-Enk were impaired in the mesenteric vasculatures of SHR. Although the relationship between opioid peptides and sympathetic tone is not fully understood, it may be possible that the regulatory disturbances of the opioid peptides on adrenergic neurotransmission could result in the increased norepinephrine release from the vascular adrenergic neurons and enhance the vascular contractility in hypertension.

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