Adrenomedullin Inhibits the Pressor Effects and Decrease in Renal Blood Flow Induced by Norepinephrine or Angiotensin II in Anesthetized Rats

Kouichiro Minami^{1,*}, Kayoko Segawa², Yasuhito Uezono³, Yosuke Shiga¹, Munehiro Shiraishi¹, Junichi Ogata¹ and Akio Shigematsu¹

¹Department of Anesthesiology and ²Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, 1-1 Iseigaoka, Yahatanishiku, Kitakyushu 807-8555, Japan

³Department of Pharmacology, Miyazaki Medical College, School of Medicine, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan

Received June 1, 2000 Accepted March 1, 2001

ABSTRACT—Adrenomedullin (AM), a hypotensive peptide originally isolated from human pheochromocytoma, has been reported to regulate renal functions. In patients with glomerulonephritis, the serum levels of AM are elevated as well as hypertensive agents norepinephrine (NE) and angiotensin II (AII). The effects of AM on the NE- or AII-induced pressor effects and renal blood flow responses, however, are not well clarified. We examined the effects of AM on blood pressure and renal blood flow induced by NE or AII in anesthetized rats. Arterial blood pressure and renal blood flow were measured using a calibrated pressure transducer and a laser Doppler flowmeter, respectively. Drugs were injected into the tail vein with a syringe. Intravenous administration of AM (1–3 nmol/kg) decreased the arterial blood pressure in anesthetized rats in a dose-dependent manner, whereas it did not affect the renal blood flow. NE or AII administration in anesthetized rats caused both increases in blood pressure and decreases in renal blood flow. Simultaneous administration of AM with NE or AII prevented the increasing effects of blood pressure and inhibited the decreases in renal blood flow caused by NE or AII. These findings suggest that AM may have a protective role against the pressor effects and decrease in renal blood flow caused by NE or AII.

Keywords: Adrenomedullin, Renal blood flow, Norepinephrine, Angiotensin II

Adrenomedullin (AM) is a hypotensive peptide that was discovered from human pheochromocytoma (1). AM and AM mRNA are widely distributed not only in pheochromocytoma but also in the adrenal medulla, ventricle, lung and kidney in human and other animals (1, 2). Studies regarding to the effects of AM on renal functions have shown that infusion of AM increases renal blood flow, arterial conductance, glomerular filtration, urine flow and sodium excretion in human and several animal models (3–5).

Several reports have pointed out that AM levels in plasma are elevated in hypertension and in chronic renal failure. Kitamura et al. found that AM levels in plasma are elevated in hypertensive patients and suggested that the peptide might exert beneficial arteriolar vasodilator effects in such conditions (6). Also, Tanaka et al. (7) and Kohno

et al. (8) reported that AM levels in the circulation are elevated in chronic renal failure patients. On the other hand, the level of the hypertensive agents norepinephrine (NE) and angiotensin II (AII) are also elevated in plasma in both hypertension and chronic renal failure (9–11). NE and AII have been reported to decrease renal blood flow (12–14), which could eventually cause renal dysfunction. It is assumed that increased circulating AM level may be a part of the compensatory mechanism in the case of hypertension and renal failure; however, it remains unknown whether AM inhibits the pressor effects and decrease in renal blood flow caused by NE or AII. In the present study, to clarify the significance of AM as a local regulator of the renal functions, we examined the effects of AM on NE- or AII-induced renal blood flow as well as blood pressure in anesthetized rats.

*Corresponding author. FAX: +81-93-601-2910

E-mail: kminami@med.uoeh-u.ac.jp

MATERIALS AND METHODS

Drugs

Drugs were obtained from the following sources: Ringer's lactate solution (Otsuka, Tokyo); AM (Peptide Institute, Osaka); NE and AII (Sigma, St. Louis, MO, USA).

Animal preparation and recording of blood pressure and renal blood flow

Adult male Wistar rats (300 g) were anesthetized with pentobarbital sodium (50 mg/kg) intraperitoneally. A polyvinyl chloride catheter was placed in the femoral artery and arterial blood pressure was measured using a calibrated pressure transducer (Baxter Healthcare, Santa Ana, CA, USA) positioned one third the distance from the brisket to the top of the back and recorded using a polygraph (Datascope 870 monitor; Datascope Corporation, Paramus, NJ, USA) and a Maclab/2 data acquisition system (AD Instruments Pty. Ltd., Castle Hill, NSW, Australia), as previously reported (15). Another catheter was inserted into the tail vein for administration of test compounds, and Ringer's lactate solution was infused at 4 ml/h with an infusion pump (SP-500; JMS, Hiroshima). Test compounds were administered within 5 s with a syringe. An incision was made to expose the left kidney and the probe of a laser Doppler flowmeter (BRC-100; Bioresearch Center, Nagoya) which was fixed on the surface of the kidney to measure the renal blood flow in the renal cortex. The data of the renal blood flow was acquired in the Maclab/2 system. Mean arterial pressure and renal blood flow in the rats were stabilized 80 to 120 min after treatment of pentobarbital sodium (data not shown). Accordingly, we started to examine the effects of several test compounds on rats 120 min after pentobarbital sodium treatment. A body temperature of 37°C was maintained with a heating pad during the experiments. This study conformed to the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institute of Health, the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society, and the Institutional Animal Care and Use Committee of the University of Occupational and Environmental Health.

Experimental protocol

After surgery and a 120-min equilibration period after pentobarbital sodium treatment of rats, we measured the arterial blood pressure and the renal blood flow for 5 min before administration of test compounds (control) and throughout the experiments. The injection of Ringer's lactate solution without test compounds caused no changes of the mean arterial blood pressure ($99.2 \pm 0.5\%$ of control, $n = 5$, N.S.) or renal blood flow ($99.0 \pm 0.4\%$ of control, $n = 5$, N.S.). The maximal changes in blood pressure and

renal blood flow were observed approximately 1–2 min after administration of each test compound. The mean blood pressure is expressed in mmHg, and the renal blood flow is expressed in mV according to the previous reports in which the same laser Doppler flowmeter was used for measuring renal blood flow (16, 17).

Statistics

Due to differences of the data among each rat to rat, the summarized results (Table 1, Fig. 2: B and C) are expressed as percentages of the control responses. All values are expressed as the mean $\pm$ S.E.M. Either a *t*-test or a one-way analysis of variance followed by a *post hoc* test (Duncan's multiple range test) was used for statistical evaluation. A value of $P < 0.05$ was considered statistically significant.

RESULTS

In anesthetized rats, intravenous administration of 1, 2 or 3 nmol/kg AM decreased the arterial blood pressure in a dose-dependent manner, and the blood pressure returned to control levels approximately 20 min after administration of AM (Table 1 and Fig. 1A), as previously reported in an *in vivo* experimental system (18–20). On the other hand, administration of the same doses of AM did not affect the renal blood flow in spite of the decreased blood pressure (Table 1 and Fig. 1B).

As a preliminary experiment, we measured the blood pressure and renal blood flow by varying doses of NE (300 ng/kg to 3 μ g/kg) and 1.7 μ g/kg NE was chosen, which caused submaximal changes (approximately 80% of the control level) of the renal blood flow. Intravenous administration of NE (1.7 μ g/kg) increased the arterial blood pressure ($133.1 \pm 13.0\%$ of the control, $n = 6$) and decreased renal blood flow ($82.9 \pm 7.5\%$ of the control, $n = 6$) (Fig. 2A). In the same anesthetized rats, NE and AM (2 nmol/kg) were injected simultaneously 60 min after NE administration. Simultaneous administration of AM (2 nmol/kg) and NE (1.7 μ g/kg) significantly inhibited the increase in the blood pressure ($115.7 \pm 5.6\%$ of the control, $n = 6$) induced by NE alone and prevented the decrease in renal blood flow ($95.2 \pm 2.4\%$ of the control, $n = 6$) caused by NE alone. Second administration of the same dose of NE alone 60 min after 1st administration of NE caused essentially similar responses as in the 1st administration of NE; second administration of NE elevated the blood pressure to $133.0 \pm 12.0\%$ of the control and decreased the renal blood flow to $86.5 \pm 3.5\%$ of the control ($n = 4$). This observation eliminates the possibility that the responses induced by NE plus AM were due to the repeated administration of the test compounds. Figure 2B summarizes the effect of AM on NE-induced blood pressure and renal blood flow.

Table 1. Dose-dependent decreases in arterial mean blood pressure but not renal blood flow induced by administration of AM in anesthetized rats

AM (nmol/kg)	Mean blood pressure (% of control)	Renal blood flow (% of control)
1	89.7 ± 3.2	98.2 ± 7.3
2	86.4 ± 5.0*	98.8 ± 1.0
3	76.5 ± 6.1**	97.9 ± 3.8

After measuring the mean arterial blood pressure and renal blood flow for 5 min (control), AM was injected into the rat tail vein and the mean arterial pressure and renal blood flow were measured over 2 min. Maximal hypotensive effects were observed approximately 1–2 min after administration of AM. Control levels of the mean blood pressure and renal blood flow rate were 100.7 ± 1.2 mmHg and 155.2 ± 4.0 mV, respectively ($n = 6$). The data obtained from 11 rats are expressed as percentages of the control values. * $P < 0.05$ and ** $P < 0.01$, as compared to control.

Fig. 1. Typical recordings of the effects of AM on arterial blood pressure and renal blood flow in anesthetized rats. AM (2 nmol/kg) was injected into the tail vein of the anesthetized rats and measured arterial blood pressure (A) and renal blood flow (B). The data of arterial blood pressure and renal blood flow are expressed in mmHg and mV, respectively.

As the case of NE, we measured the blood pressure and renal blood flow induced by varying doses of AII (33–200 ng/kg) and a dose that causes submaximal responses (100 ng/kg) was chosen. Intravenous administration of AII (100 ng/kg) increased the blood pressure ($114.1 \pm 7.2\%$ of the control, $n = 6$) and persistently decreased the renal blood flow for up to 20–30 min after AII administration ($76.0 \pm 6.4\%$ of the control, $n = 6$) (Fig. 3A). AM (2 nmol/kg), when simultaneously administered with AII (100 ng/kg) 60 min after 1st administration of AII, abrogated the pressor effect of AII ($99.6 \pm 0.4\%$ of the control, $n = 6$) and inhibited the renal blood flow ($87.2 \pm 2.5\%$ of the control,

Fig. 2. Effects of AM on the NE-induced elevation in arterial blood pressure and decrease in renal blood flow in anesthetized rats. A: Typical recordings of the effects of NE on the arterial blood pressure and renal blood flow in anesthetized rats. NE ($1.7 \mu\text{g/kg}$) was administered and the arterial blood pressure and renal blood flow were measured. B: Summary of the effects of AM on the NE-induced elevation in arterial blood pressure and decrease in renal blood flow in anesthetized rats. NE ($1.7 \mu\text{g/kg}$) alone or NE plus AM (2 nmol/kg)-induced arterial blood pressure and renal blood flow were measured. NE and AM (2 nmol/kg) were administered simultaneously 60 min after administration of NE alone. The data obtained from 6 anesthetized rats are expressed as percentages of the control values. * $P < 0.05$, as compared to the control. N.S., not significantly different as compared to the control.

$n = 6$) induced by AII. Second administration of the same dose of AII 60 min after 1st administration of AII caused essentially similar responses as in the 1st administration of AII; it elevated the blood pressure to $111.0 \pm 6.6\%$ of the control and decreased the renal blood flow to $79.0 \pm 4.0\%$ of the control ($n = 4$). This observation again suggest that the responses induced by AM and AII were not due to the repeated administration of the test compounds. Figure 3B summarizes the effect of AM on AII-induced blood pressure and renal blood flow.

DISCUSSION

Our main finding in the present study is that AM inhibited both increase in blood pressure and decrease in blood flow induced by NE or AII in anesthetized rats. Circulating

Fig. 3. Effects of AM on the AII-induced arterial blood pressure and renal blood flow in anesthetized rats. A: Typical recordings of the effects of AII on the arterial blood pressure and renal blood flow in anesthetized rats. AII (100 ng/kg) was administered and the arterial blood pressure and renal blood flow were measured. B: Summary of the effects of AM on the AII-induced arterial blood pressure and renal blood flow in anesthetized rats. AII (100 ng/kg) alone or AII plus AM (2 nmol/kg)-induced arterial blood pressure and renal blood flow were measured. AII plus AM (2 nmol/kg) were administered simultaneously 60 min after administration of AII alone. The data obtained from 6 anesthetized rats are expressed as percentages of the control values. * $P < 0.05$ and ** $P < 0.01$, as compared to the control. N.S., not significantly different as compared to the control.

catecholamines or sympathetic autonomic innervation of the kidney influence renal functions as well as vascular constriction via activation of renal adrenergic receptors. NE infusion or renal nerve stimulation reduces the renal blood flow (12). The present study showed that AM prevented the elevation of NE-induced blood pressure and inhibited the NE-induced decrease in renal blood flow. AM is reported to be present and released from renal glomerular and tubular cells (21, 22). Our results favor the view that AM released from the kidney may prevent the vasoconstriction of arteries caused by NE and thus regulate the renal blood flow possibly in a paracrine manner.

AII, the most potent hypertensive peptide that activates the renin-angiotensin system, plays an important role in regulating renal hemodynamics and urine formation. Exogenous infusion of AII decreases renal blood flow in humans (13, 23) and in animal models (14, 24). We found that AM

inhibited both the increase in blood pressure and decrease in renal blood flow induced by AII, suggesting that AM could prevent the AII-induced contraction of these arteries and the subsequent decrease in renal blood flow in a paracrine manner, as in the case of NE. Recently, AM is reported to attenuate the pressor responses to AII by preventing the increase in peripheral resistance induced by AII in conscious sheep (25). The result and our findings suggest that AM prevents the increase in peripheral resistance induced by AII, thereby inhibiting the decrease in renal blood flow in the kidney.

The intracellular mechanism of action of AM remains controversial. The main intracellular second messenger for AM is considered to be cAMP and AM causes vasodilatation by increasing cAMP levels in vascular smooth muscle cells (26, 27). Recent reports have shown, however, that AM receptor stimulation is also linked to the activation of the phospholipase C pathway and nitric oxide synthase (NOS) pathway. In bovine endothelial cells, AM increases both cAMP and intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$), and increased $[\text{Ca}^{2+}]_i$ activates NOS to release NO (28). NO is reported to be an important second messenger in regulating AM-induced renal vasodilation in the rat and dog kidney (29, 30). On the other hand, AM is reported to decrease $[\text{Ca}^{2+}]_i$ in the rat renal smooth muscle cells followed by the inhibition of vasoconstriction induced by agents that increase $[\text{Ca}^{2+}]_i$ such as the α_1 -adrenergic agonist phenylephrine (31). Charles et al. proposed that AM-induced inhibition of peripheral resistance caused by AII may be mediated through opposing effects of AII at the intracellular Ca^{2+} levels in the cells (25). Although precise mechanisms by which AM inhibits the NE- or AII-induced pressor effects and decrease in renal blood flow remains to be elucidated, it is conceivable that AM may have opposing effects against NE or AII at the intracellular second messenger levels.

The renal cortex is mostly composed of glomeruli, which almost supplies blood flow to the kidney (32). In our study, we measured the renal blood flow in the renal cortex and showed that AM inhibited the AII- or NE-induced decrease in blood flow of glomeruli. According to the studies with a renal microvessel preparation, NE caused contraction of the interlobular, efferent and afferent arteries (33, 34), thereby resulting in the decrease of renal blood flow. In addition, these arteries are also sensitive to AII to cause vasoconstriction; in particular, afferent arteries are more sensitive to AII than the interlobular and efferent arteries (33, 35–37). Our results and their reports suggest that AM functions at the interlobular, efferent and afferent arteries to cause vasodilatation and thus inhibits the AII- or NE-induced decrease in glomerular filtration rate. This is supported by the finding that AM caused vasodilatation of isolated afferent arteries in rabbits (38).

In summary, we demonstrated that AM administration inhibits both the pressor effects and decrease in the renal blood flow induced by NE or AII in anesthetized rats. These findings suggest that AM may have a compensatory role against hypertension and renal failure, which could be caused by elevation of NE or AII levels in plasma in such pathophysiological conditions. AM may be a useful agent to prevent the pathological progression of renal disorder.

Acknowledgment

This research was supported by Grants-in-Aid (10770539, 11671532, 10770778, 11770878) from the Ministry of Education, Science Sports and Culture of Japan and the Japanese Foundation for Cardiovascular Research.

REFERENCES

- Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H and Eto T: Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun* **192**, 553 – 560 (1993)
- Kitamura K, Sakata J, Kangawa K, Kojima M, Matsuo H and Eto T: Cloning and characterization of cDNA encoding a precursor for human adrenomedullin. *Biochem Biophys Res Commun* **194**, 720 – 725 (1993)
- Ebara T, Miura K, Okumura M, Matsuura T, Kim S, Yukimura T and Iwao H: Effect of adrenomedullin on renal hemodynamics and function in dogs. *Eur J Pharmacol* **263**, 69 – 73 (1994)
- Elhawary AM, Poon J and Pang CC: Effects of calcitonin gene-related peptide receptor antagonists on renal actions of adrenomedullin. *Br J Pharmacol* **115**, 1133 – 1140 (1995)
- Vari RC, Adkins SD and Samson WK: Renal effects of adrenomedullin in the rat. *Proc Soc Exp Biol Med* **211**, 178 – 183 (1996)
- Kitamura K, Ichiki Y, Tanaka M, Kawamoto M, Emura J, Sakakibara S, Kangawa K, Matsuo H and Eto T: Immunoreactive adrenomedullin in human plasma. *FEBS Lett* **341**, 288 – 290 (1994)
- Tanaka M, Kitamura K, Ishizaka Y, Ishiyama Y, Kato J, Kangawa K and Eto T: Plasma adrenomedullin in various diseases and exercise-induced change in adrenomedullin in healthy subjects. *Intern Med* **34**, 728 – 733 (1995)
- Kohno M, Hanehira T, Kano H, Horio T, Yokokawa K, Ikeda M, Minami M, Yasunari K and Yoshikawa J: Plasma adrenomedullin concentrations in essential hypertension. *Hypertension* **27**, 102 – 107 (1996)
- Brown JJ, Fraser R, Leckie B, Lever AF, Morton JJ, Padfield PL, Semple PF and Robertson JJ: Significance of renin and angiotensin in hypertension. *Cardiovasc Clin* **9**, 55 – 89 (1978)
- Ishii M, Ikeda T, Takagi M, Sugimoto T, Atarashi K, Igari T, Uehara Y, Matsuoka H, Hirata Y, Kimura K, Takeda T and Murao S: Elevated plasma catecholamines in hypertensives with primary glomerular diseases. *Hypertension* **5**, 545 – 551 (1983)
- Darwish R, Elias AN, Vaziri ND, Pahl M, Powers D and Stokes JD: Plasma and urinary catecholamines and their metabolites in chronic renal failure. *Arch Intern Med* **144**, 69 – 71 (1984)
- DiSalvo J and Fell C: Changes in renal blood flow during renal nerve stimulation. *Proc Soc Exp Biol Med* **136**, 150 – 153 (1971)
- Hollenberg NK, Williams GH, Burger B, Chenitz W, Hoosmand I and Adams DF: Renal blood flow and its response to angiotensin II. An interaction between oral contraceptive agents, sodium intake, and the renin-angiotensin system in healthy young women. *Circ Res* **38**, 35 – 40 (1976)
- Rosivall L and Navar LG: Effects on renal hemodynamics of intra-arterial infusions of angiotensin I and II. *Am J Physiol* **245**, F181 – F187 (1983)
- Minami K, Yanagihara N, Segawa K, Sata T, Tsutsui M, Shigematsu A and Izumi F: Inhibition by protamine of catecholamine secretion and ion influxes in bovine adrenal medullary cells in culture. *J Pharmacol Exp Ther* **279**, 838 – 843 (1996)
- Wada K, Kamisaki Y, Kitano M, Nakamoto K and Itoh T: Protective effect of cystathionine on acute gastric mucosal injury induced by ischemia-reperfusion in rats. *Eur J Pharmacol* **294**, 377 – 382 (1995)
- Wada K, Kamisaki Y, Kitano M, Kishimoto Y, Nakamoto K and Itoh T: A new gastric ulcer model induced by ischemia-reperfusion in the rat: role of leukocytes on ulceration in rat stomach. *Life Sci* **59**, PL295 – PL301 (1996)
- Nuki C, Kawasaki H, Kitamura K, Takenaga M, Kangawa K, Eto T and Wada A: Vasodilator effect of adrenomedullin and calcitonin gene-related peptide receptors in rat mesenteric vascular beds. *Biochem Biophys Res Commun* **196**, 245 – 251 (1993)
- Hao Q, Chang JK, Gharavi H, Fortenberry Y, Hyman A and Lipton H: An adrenomedullin (AM) fragment retains the systemic vasodilator activity of human adrenomedullin. *Life Sci* **54**, PL265 – PL270 (1994)
- Haynes JM and Cooper ME: Adrenomedullin and calcitonin gene-related peptide in the rat isolated kidney and in the anaesthetised rat: in vitro and in vivo effects. *Eur J Pharmacol* **280**, 91 – 94 (1995)
- Jougasaki M, Wei CM, Aarhus LL, Heublein DM, Sandberg SM and Burnett JC Jr: Renal localization and actions of adrenomedullin: a natriuretic peptide. *Am J Physiol* **268**, F657 – F663 (1995)
- Michibata H, Mukoyama M, Tanaka I, Suga S, Nakagawa M, Ishibashi R, Goto M, Akaji K, Fujiwara Y, Kiso Y and Nakao K: Autocrine/paracrine role of adrenomedullin in cultured endothelial and mesangial cells. *Kidney Int* **53**, 979 – 985 (1998)
- Hollenberg NK, Solomon HS, Adams DF, Abrams HL and Merrill JP: Renal vascular responses to angiotensin and norepinephrine in normal man. Effect of sodium intake. *Circ Res* **31**, 750 – 757 (1972)
- Chatziantoniou C, Daniels FH and Arendshorst WJ: Exaggerated renal vascular reactivity to angiotensin and thromboxane in young genetically hypertensive rats. *Am J Physiol* **259**, F372 – F382 (1990)
- Charles CJ, Rademaker MT, Richards AM, Cooper GJS, Coy DH and Nicholls MG: Adrenomedullin attenuates pressor response to angiotensin II in conscious sheep. *J Cardiovasc Pharmacol* **36**, 526 – 532 (2000)
- Eguchi S, Hirata Y, Kano H, Sato K, Watanabe Y, Watanabe TX, Nakajima K, Sakakibara S and Marumo F: Specific receptors for adrenomedullin in cultured rat vascular smooth muscle cells. *FEBS Lett* **340**, 226 – 230 (1994)
- Ishizaka Y, Ishizaka Y, Tanaka M, Kitamura K, Kangawa K, Minamino N, Matsuo H and Eto T: Adrenomedullin stimulates cyclic AMP formation in rat vascular smooth muscle cells.

- Biochem Biophys Res Commun **200**, 642 – 646 (1994)
- 28 Shimekake Y, Nagata K, Ohta S, Kambayashi Y, Teraoka H, Kitamura K, Eto T, Kangawa K and Matsuo H: Adrenomedullin stimulates two signal transduction pathways, cAMP accumulation and Ca^{2+} mobilization in bovine aortic endothelial cells. *J Biol Chem* **270**, 4412 – 4417 (1995)
 - 29 Hirata Y, Hayakawa H, Suzuki Y, Ikenouchi H, Kohmoto O, Kimura K, Kitamura K, Eto T, Kangawa K, Matsuo H and Omata M: Mechanism of adrenomedullin-induced vasodilatation in the rat kidney. *Hypertension* **25**, 790 – 795 (1995)
 - 30 Miura K, Ebara T, Okumura M, Matsuura T, Kim S, Yukimura T and Iwao H: Attenuation of adrenomedullin-induced renal vasodilatation by N^G -nitro L-arginine but not glibenclamide. *Br J Pharmacol* **115**, 917 – 924 (1995)
 - 31 Seguchi H, Nishimura J, Kobayashi S, Kumazawa J and Kanaide H: Autocrine regulation of the renal arterial tone by adrenomedullin. *Biochem Biophys Res Commun* **215**, 619 – 625 (1995)
 - 32 Aronson S and Blumenthal R: Perioperative renal dysfunction and cardiovascular anesthesia: concerns and controversies. *J Cardiothorac Vasc Anesth* **12**, 567 – 586 (1998)
 - 33 Edwards RM: Segmental effects of norepinephrine and angiotensin II on isolated renal microvessels. *Am J Physiol* **244**, F526 – F534 (1983)
 - 34 Wilson SK: The effects of angiotensin II and norepinephrine on afferent arterioles in the rat. *Kidney Int* **30**, 895 – 905 (1986)
 - 35 Ito S, Johnson CS and Carretero OA: Modulation of angiotensin II-induced vasoconstriction by endothelium-derived relaxing factor in the isolated microperfused rabbit afferent arteriole. *J Clin Invest* **87**, 1656 – 1663 (1991)
 - 36 Carmines PK, Morrison TK and Navar LG: Angiotensin II effects on microvascular diameters of in vitro blood-perfused juxtamedullary nephrons. *Am J Physiol* **251**, F610 – F618 (1986)
 - 37 Yuan BH, Robinette JB and Conger JD: Effect of angiotensin II and norepinephrine on isolated rat afferent and efferent arterioles. *Am J Physiol* **258**, F741 – F775 (1990)
 - 38 Kawabe T, Shiotani M, Hano T, Baba A, Nakamura Y, Booka Ssatani Y, Wanaka Y, Kasamatsu K and Nishio I: The mechanism of adrenomedullin-induced vasodilation on isolated and microperfused renal afferent arterioles in the rabbit. *J Hypertension Suppl* **2**, **16**, S8 (1998)