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Effects of intrarenal arterial infusion of Russell's vipervenom on renal hemodynamics, plasma renin activity,and plasma thromboxane B2 in indomethacin plusenalapril pretreated dogs.

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Effects of intrarenal arterial infusion of Russell's viper venom on renal hemodynamics, plasma renin activity, and plasma thromboxane B_2 in indomethacin plus enalapril pretreated dogs.

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Background : *Renal failure is common in Russell's viper envenomation. Previous studies revealed the decreases in blood pressure (BP) and total peripheral resistance (TPR). Renal vascular resistance (RVR) was increased resulting in reduction of renal blood flow (RBF) and glomerular filtration rate (GFR). These changes might be attributed to the release of prostaglandins (PGs), thromboxane A_2 (TXA_2) and renin-angiotensin stimulation (RAS).*

Objective : *In order to elucidate the roles of PGs, TXA_2 and Angiotensin II on renal hemodynamic changes induced by Russell's viper venam (RVV), the RVV was directly given into the renal artery, and the effect of indomethacin and enalapril pretreatment on renal hemodynamics, plasma renin activity (PRA) and plasma thromboxane B_2 (P_{TXB_2}) were studied in dogs.*

Design : *Experimental study, before-after with control group.*

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Material and Method : *Twelve male mongrel dogs were divided into 2 groups. In group I (N = 6), RVV (1.25 μg/kg/min) was infused directly into the renal artery. In group II, six dogs were pretreated with indomethacin (5 mg/kg, iv) and enalapril (5 mg/kg, iv) before the RVV infusion (1.25 μg/kg/min). All parameters were determined every 20 min before and after RVV infusion.* P_{TXB_2} *and PRA were measured by radioimmunoassay. The paired t-test and analysis of variance were used in analysing the data.*

Results : *The direct infusion of RVV into the renal artery caused a reduction of mean arterial pressure (MAP), but the RBF and GFR remained unchanged, and urine flow rate (V) was increased. RVR was decreased, fractional excretion of Na* (FE_{Na}) *was increased, and* P_{TXB_2} *was increased, whereas PRA was slightly decreased. After the indomethacin and enalapril injection, the direct infusion of RVV caused reduction of RBF and V, GFR was initially decreased and returned toward the pretreatment value, RVR was increased, and* P_{TXB_2} *and PRA were decreased. However, the MAP remained unchanged.*

Conclusions : *The results indicated that RVV given directly into the renal artery caused renal vasodilation. This effect was prostaglandin mediated since indomethacin which inhibits prostaglandin systhesis, decreased RBF and GFR. The increase in* P_{TXB_2} *might cause vasoconstriction but was overcome by the effect of prostaglandins, which was not measured in this study. The increase in PRA in group II might be secondary to the decrease in RBF in order to maintain the GFR. However, enalapril, which inhibits the conversion of angiotensin I (AI) into angiotensin II (AII), partly inhibited the increase in GFR. The RVV itself may possess the activity of a converting enzyme and thus converts the AI into AII and attenuates the effect of enalapril.*

Key words : *Russell's viper venom, Plasma renin activity, Thromboxane, Indomethacin, Enalapril.*

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โสภิต ธรรมอารี, วิศิษฏ์ สิตปรีชา, ณรงค์ศักดิ์ ชัยบุตร, สมัย ลีพิพัฒน์ไพบูลย์, ชลดา บูรณกาล. ฤทธิ์ของพิษงูแมวเซาที่ฉีดเข้าหลอดเลือดแดงของไตต่อหน้าที่ของไต แอกทิวิตี้ของเรนินในพลาสมา และระดับธรอมบ๊อกเซนบีทูในพลาสมาในสุนัขที่ได้รับอินโดเมธาซินและอินาลาพริล. จุฬาลงกรณ์เวชสาร 2542 มี.ค; 43(3): 147-57

วัตถุประสงค์ : *เพื่ออธิบายบทบาทของพรอสทาแกลนดิน ธรอมบ๊อกเซนเอทู และแองจิโอเทนซินทู ในการเปลี่ยนแปลงหน้าที่ของไตที่เกิดจากพิษงูแมวเซาที่ให้โดยตรงเข้าหลอดเลือดแดงของไต และผลของยาอินโดเมธาซินและอินาลาพริลที่ให้ก่อนการฉีดพิษงูแมวเซา*

สถานที่ทำการศึกษา : *ภาควิชาเภสัชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

รูปแบบการวิจัย : *การวิจัยเชิงทดลองแบบวัดผลก่อนและหลังและมีกลุ่มควบคุม*

วิธีการศึกษา-วัดผล : *สุนัขพันธุ์ผสมเพศผู้จำนวน 12 ตัว แบ่งออกเป็น 2 กลุ่ม ศึกษา กลุ่มที่ 1 (สุนัข 6 ตัว) ฉีดพิษงูแมวเซา (1.25 ไมโครกรัม/กิโลกรัม/นาที) เข้าหลอดเลือดแดงที่ไตโดยตรง กลุ่มที่ 2 สุนัข 6 ตัว ได้รับอินโดเมธาซิน (5 มิลลิกรัม/กิโลกรัม เข้าหลอดเลือดดำ) และอินาลาพริล (5 มิลลิกรัม/กิโลกรัม เข้าหลอดเลือดดำ) ก่อนการฉีดพิษงูแมวเซา วัดตัววัดทุกชนิดทุกๆ 20 นาที ก่อนและหลังการฉีดพิษงูแมวเซา หาระดับธรอมบ๊อกเซนบีทูและแอกทิวิตี้ของเรนินในพลาสมาด้วยวิธีเรดิโออิมมิวโน แอสเส วิเคราะห์ข้อมูลโดยใช้ paired t-test และ analysis of variance*

ผลการศึกษา : *การฉีดพิษงูแมวเซาเข้าหลอดเลือดแดงของไต ทำให้ความดันโลหิตลดลงแต่เลือดที่ไปยังไตและการกรองที่ไตไม่เปลี่ยนแปลง อัตราการไหลของปัสสาวะเพิ่มขึ้น ความต้านทานในหลอดเลือดแดงที่ไตลดลงและเพิ่มการขับถ่ายโซเดียม ระดับ ธรอมบ๊อกเซนบีทูในพลาสมาเพิ่มขึ้นและแอกทิวิตี้ของเรนินในพลาสมาลดลงเล็กน้อยส่วนการฉีดพิษงูแมวเซาหลังจากให้อินโดเมธาซินและอินาลาพริลแล้วทำให้ความดันโลหิตไม่เปลี่ยนแปลงเลือดที่ไปยังไตลดลงการกรองที่ไตในระยะแรกลดลงแล้วกลับคืนสู่ระดับปกติ อัตราการไหลของปัสสาวะลดลง ระดับธรอมบ๊อกเซนบีทูในพลาสมาลดลงและแอกทิวิตี้ของเรนินในพลาสมาลดลงจากระยะที่ให้อินาลาพริลไปแล้ว*

วิจารณ์และสรุป : *ผลการศึกษาบ่งชี้ว่าพิษงูแมวเซาที่ให้โดยตรงเข้าหลอดเลือดแดงของไต ทำให้หลอดเลือดแดงที่ไตขยายตัว ผลนี้เกิดจากพรอสทาแกลนดิน เพราะอินโดเมธาซินซึ่งยับยั้งการสังเคราะห์พรอสทาแกลนดิน ทำให้เลือดที่ไปยังไตและการกรองที่ไตลดลง การเพิ่มธรอมบ็อกเซนบีทูอาจทำให้หลอดเลือดหดตัวแต่ความดันโลหิตลดลง แสดงว่าผลนี้ถูกเอาชนะได้โดยพรอสทาแกลนดินที่มีฤทธิ์ขยายหลอดเลือด การเพิ่มแอกทิวิตี้ของเรนินในพลาสมาเป็นผลมาจากการลดเลือดไปยังไต เพื่อเพิ่มการกรองที่ไต และเป็นผลมาจากอินาลาพริล แต่เมื่อให้พิษงูแมวเซาทำให้แอกทิวิตี้ของเรนินในพลาสมาลดลงอาจเนื่องจากพิษงูแมวเซามีส่วนประกอบที่มีฤทธิ์เป็น converting enzyme และเปลี่ยนแองจิโอเทนซินวันเป็นแองจิโอเทนซินทูจึงลดฤทธิ์ของอินาลาพริ ล*

Renal failure is one of the principal effects of Russell's viper poisoning in humans and is responsible for most of the deaths occurring a few days after the bite.[1-3] It is of great practical importance to determine the mechanism of this renal failure. Previous reports have revealed that in most instances renal ischemia very likely contributes to renal failure and tubular necrosis. This might result from hypotension, shock, disseminated intravascular coagulation or renal vasoconstriction[2, 4, 5] Some clinical evidence, as well as several in vitro studies have also suggested direct nephrotoxicity of the venom.[4,6-10] It has been proposed that many pharmacologically active substances might be liberated by RVV. Released catecholamines, renin-angiotensin activation[5, 11] and released prosta glandins[10,12] might somehow interact and thus be responsible for the changes in blood pressure and renal hemodynamics induced by RVV. Previous reports, so far, have shown the effects of phospholipase A_2 isolated from RVV on plasma prostacyclin levels and plasma renin activity.[13, 14] When the venom was injected into the vein, systemic hypotension and renin angiotensin activation were observed[13] The increased RVR resulted in decreased renal perfusion. To obtain the direct effects of RVV on renal hemodynamics, the present study was designed to administer the RVV directly into the renal artery, and studied the roles of PGs, TXA_2 and the renin-angiotensin system in mediating the renal hemodynamic effects of RVV by using indomethacin, a cyclooxygenase inhibitor, and enalapril, an angiotensin converting enzyme inhibitor. Measurement of P_{TXB_2}, a stable metabolite of TXA_2, and PRA would reveal the changes of plasma TXA_2 and renin during RVV injection and confirm the effects of the indomethacin and enalapril. The results of this study may define the mechanisms underlying RVV effects and this may be useful for the development of new pharmacological interventions against RVV associated ophidism.

Materials and Methods

Twelve male mongrel dogs weighing 10-15 kg were used in this study. They were anesthetized with pentobarbital sodium (25 mg/kg). Supplementary doses of 25-50 mg were given as necessary to maintain the anesthetic state throughout the study. The dogs were fasted overnight but were allowed free access to water. In all dogs the femoral artery for blood sample collection and for recording of blood pressure and heart rate (HR) was cannulated on a Grass Physiograph. The femoral vein was cannulated for normal saline infusion and continual sustaining inulin and p-aminohippuric acid (PAH) infusion for the renal hemodynamic studies. A curved 23 gauge needle attached to polyethylene tube was inserted at the origin of renal artery connected with syringe pump running 0.5 ml/min with normal saline solution and for direct intra-arterial venom infusion. Urine was collected from the respective kidney by bladder catheterization. A priming dose of PAH and inulin was given intravenously followed by continuous infusion of these substances at the rate of 1.6 ml/min to achieve plasma levels of approximately 0.03 mg/ml and 0.20 mg/ml of PAH and inulin, respectively. RVV in lyophilized form was produced and supplied by the Science Division of the Thai Red Cross Society.

Experiment Design

The experiments were conducted in two groups of 6 dogs each. During the control period of 60 min, normal saline solution (NSS) was administered into the

renal artery through the cannula at rate of 0.5 ml/min. **In group 1**, this was switched to a solution of 0.05 mg of RVV/kg body weight in 20 ml of NSS infused into the renal artery at a rate of 0.5 ml/min over a period of 40 min and followed by NSS infusion at the same rate for 20 min. **In group 2**, following a control period of 60 min, indomethacin (5 mg/kg) dissolved in 2.0 ml of 1% $NaHCO_3$ solution was given intravenously and followed by NSS infusion at a rate of 1 ml/min for 40 min, then enalapril (5 mg/kg) was given intravenously followed by NSS infusion at the rate of 1 ml/min for 40 min during which intrarenal NSS was given at the rate of 0.5 ml/min. After this period, intrarenal arterial infusion of RVV (0.5 mg/kg) in NSS was started. After a period of 40 min, NSS was infused at the same rate for 20 min.

Every 20 min, determinations were made of MAP, HR, renal hemodynamics including renal blood flow (RBF), glomerular filtration rate (GFR), urine flow rate (V), renal vascular resistance (RVR), fractional excretion of sodium (FE_{Na}), FE_K and FE_{Cl} , and plasma concentrations of thromboxane B_2 (TXB_2), a stable metabolite of thromboxane A_2 (TXA_2), and plasma renin activity.

Techniques and Calculations

Mean arterial pressure (MAP) was calculated from the systolic blood pressure (SBP) and diastolic blood pressure (DBP). Renal plasma flow (RPF) and GFR were measured as a function of PAH and inulin clearances using standard techniques.[15] Plasma and urine concentrations of inulin and PAH were measured by methods described by Davidson and Sackner[16] and Smith.[17] RBF was calculated from RPF and packed cell volume. RVR was calculated from MAP and RBF. Sodium and potassium were measured by flame photometry (Klina Flame, Beckman). Chloride was measured by a chloride analyser (Instrumentation Labs., model 279). Plasma renin activity was determined by measurement of angiotensin I generated by activity of the renin in the plasma. Plasma concentrations of TXB_2 and angiotensin I were measured by a radioimmunoassay method using commercially available assay kits (New England Nuclear, Du Pont Company) as described.[18,19]

Statistical Analysis

All values were expressed as mean ± SD. The data were analysed by Student's paired T test. For differences between groups, non-parametric, Kruskal-Wallis 1-Way Anova was used.[20] A p-value of < 0.05 was considered significant.

Results

Effects of intrarenal arterial injection of RVV

Table 1 summarizes the effects of RVV, given directly into the renal artery, on MAP, overall kidney functions and plasma level of TXB_2, and plasma renin activity (PRA). Reduction of MAP was observed after intrarenal arterial injection of RVV, but RBF and GFR remained unchanged. There was a rise in V in response to the RVV. RVR was decreased during RVV injection. FE_{Na} was increased during the period of venom injection and then declined toward the control level. FE_K and FE_{Cl} were changed similar to FE_{Na}. A significant increase of P_{TXB_2} was observed throughout the experiment. PRA initially declined upon RVV injection and then increased toward the control level.

Table 1. Effects of intrarenal arterial injection of RVV on MAP, renal hemodynamics, plasma thromboxane B_2 (P_{TXB_2}), and plasma renin activity (PRA) in 6 dogs.

Parameters	Control	RVV		NSS
	60 min	20 min	40 min	20 min
HR, beats/min	154 ± 11	147 ± 9	135 ± 10	135 ± 12
MAP, mmHg	128 ± 9	118 ± 10**	115 ± 15*	118 ± 14*
RBF, ml/min	96.79 ± 26.68	108.52 ± 21.47	100.85 ± 27.88	90.75 ± 22.39
GFR, ml/min	19.43 ± 5.86	17.57 ± 7.16	19.69 ± 6.3	19.12 ± 7.70
V, µl/min	434.04 ± 239.45	563.30 ± 330.79*	610.05 ± 278.64*	515.19 ± 296.50*
RVR, dyne-sec/cm^5	117,620 ± 47,696	87,853 ± 48,452**	74,207 ± 30,385**	114,628 ± 53,685
FE_{Na}, %	1.81 ± 0.97	3.25 ± 1.19***	3.73 ± 1.28***	2.48 ± 1.01
FE_K, %	23.53 ± 15.05	32.61 ± 17.03	20.15 ± 9.92	23.10 ± 8.59
FE_{Cl}, %	2.32 ± 2.86	4.33 ± 4.76*	2.52 ± 2.05	1.70 ± 1.18
P_{TXB_2}, pg/ml	122.27 ± 72.48	241.91 ± 44.89**	341.46 ± 118.33**	397.07 ± 119.07***
PRA, ng/ml/h	3.54 ± 0.87	2.32 ± 0.57	3.18 ± 1.01	2.69 ± 0.82

Values are mean ± SD, the values represent from the left kidney.

*p < 0.05, when compared with the control, ** p < 0.01, *** p < 0.001,

Effects of RVV injected into the renal artery in dogs pretreated with indomethacin plus enalapril

As summarized in table 2, a reduction of MAP during the period of RVV injection was inhibited by indomethacin plus enalapril pretreatment. Indomethacin caused a significant decrease in RBF which remained at low levels upon enalapril and RVV injection. GFR was significantly decreased after 20 min of indomethacin treatment but increased to 90% of the control level during the following 20 min . After 20 min of enalapril treatment, GFR was slightly increased and declined significantly during RVV injection. V was decreased by indomethacin treatment and rose to approximately 70% of the control level after enalapril treatment, then declined during RVV injection. RVR was increased after indomethacin treatment which slightly declined afterward upon enalapril treatment and increased again during RVV injection. Indomethacin tended to decrease FE_{Na}, FE_K and FE_{Cl} which then rose after enalapril treatment and during RVV injection. Plasma TXB_2 was decreased by indomethacin treatment and thereafter. PRA tended to increase by enalapril treatment and slightly declined afterward upon RVV injection.

Table 2. Effects of RVV, injected into the renal artery, on MAP, renal hemodynamics, plasma TXB2 and plasma renin activity (PRA) in indomethacin plus enalapril pretreatment dogs (n = 6).

Parameters	Control	Indomethacin		Enalapril				
		NSS		NSS		RVV		NSS
	60 min	20 min	40 min	20 min	40 min	20 min	40 min	20 min
HR, beats/min	165 ± 25	161 ± 25	150 ± 23	160 ± 22	161 ± 25	167 ± 28	174 ± 25	172 ± 23
MAP, mmHg	94 ± 25	109 ± 21	114 ± 16	96 ± 25	93 ± 25	89 ± 27	100 ± 39	101 ± 23
RBF, ml/min	113.85 ± 33.35	51.74 ± 14.55*	57.86 ± 26.65*	59.55 ± 16.99*	62.07 ± 32.43*	50.60 ± 23.89*+	60.57 ± 28.66*+	59.26 ± 23.72*
GFR, ml/min	18.64 ± 6.24	10.95 ± 4.16*	16.67 ± 6.07	20.05 ± 4.80	18.30 ± 7.90	9.97 ± 3.02*+	12.82 ± 5.67	14.78 ± 4.19
V, µl/min	391.69 ± 154.32	258.51 ± 83.08*	151.28 ± 77.13*	279.20 ± 56.10*	273.83 ± 114.66*	209.99 ± 104.99*	161.31 ± 6.25*	177.72 ± 42.45*
RVR, dyne-sec/cm^5	68,303 ± 17,499	178,515 ± 55,019	175,156 ± 52,881	135,966 ± 53,524	137,405 ± 58,068	156,441 ± 68,425	143,046 ±125,227	147,948 ± 76,461
FE_{Na} %	2.42 ± 0.83	2.16 ± 0.65	1.66 ± 0.74	3.51 ± 1.38	3.38 ± 1.42	3.51 ± 1.69	4.27 ± 1.18	2.01 ± 0.93
FE_K %	22.65 ± 10.15	26.20 ± 12.60	16.1 ± 6.20	17.60 ± 4.40	23.3 ± 7.3	26.6 ± 10.2	18.9 ± 5.9	20.16 ± 9.07
FE_{Cl} %	2.50 ± 0.91	2.15 ± 0.76	1.53 ± 0.62	3.40 ± 1.19	3.30 ± 1.33	3.39 ± 1.54	4.20 ± 1.1	2.25 ± 0.85
P_{TXB_2}, pg/ml	118.28 ± 104.73	83.47 ± 67.91	43.40 ± 31.46	35.74 ± 36.50	32.01 ± 30.38	20.36 ± 18.20	16.60 ± 14.64	22.73 ± 15.26
PRA, ng/ml/h	3.97 ± 3.36	3.66 ± 2.54	4.18 ± 2.78	9.2 ± 6.11	16.62 ± 12.56	11.73 ± 8.57	6.93 ± 1.65*	4.72 ± 2.58

Values are mean ± SD, the values represent from the left kidney.

* $p < 0.05$, when compared with the control period, + $p < 0.05$, when compared with the control group

Discussion

The results demonstrate that intrarenal arterial infusion of RVV in group 1 dogs decreased blood pressure, however RBF and GFR remained unchanged. This would indicate that RVV caused renal vasodilatation. This renal vasodilating effect was likely related to prostaglandins and the renin-angiotensin system since pretreatment with indomethacin and enalapril followed by RVV infusion into the renal artery in group 2 dogs prevented the decrease in MAP but decreased RBF and GFR. It is well established that indomethacin, which inhibits cyclooxygenase enzyme and thus the prostaglandin synthesis, decreases RBF and GFR.[21, 22] Whereas enalapril, an angiotensin converting enzyme inhibitor, is a vasodilator and possesses the reno-protective effect by dilating renal efferent arterioles and decreases intraglomerular pressure.[23, 24] The finding in group 2 dogs confirms the effect of indomethacin on RBF and GFR. Enalapril given after indomethacin clearly shows a hypotensive effect, thereby it decreases blood pressure in the preglomerular vessels and stimulates renin release as seen by the increase in PRA. However, inhibiting the conversion of AI into AII by enalapril could not increase the blood pressure. In spite of the decrease in RBF, the glomerular filtration rate seems to be restored, thus the smaller reduction of urine flow rate. Whether other vasoconstrictors like adenosine, endothelin released intrarenally as well as norepinephrine preferably constrict the efferent arterioles in order to regulate the GFR remains to be elucidated. RVV injected into the renal artery following indomethacin and enalapril pretreatment caused more decreases in RBF and GFR and V. It is possible that RVV produced a renal vasoconstricting effect which is not mediated by TXA_2 as found in the decrease in P_{TXB_2}. Under the inhibitory effect of enalapril on the conversion of AI into AII, it is expected to have high PRA but the RVV decreased the PRA. It is possible that AII is generated by the action of RVV-containing enzymes which have activity similar to angiotensin converting enzymes in the body. This finding suggests further study is needed. As an alternative explanation, the sympathetic activity might be activated as the blood pressure was initially decreased, or as the result secondary to the increased AII. The increase of RVR indicates renal vasoconstriction which may be the result of norepinephrine as well as AII. The renal vasoconstriction via RVV-liberated agents, like adenosine extruded by damaged cells[25] or via a reduced NO-production resulting from endothelial cell damage[26] cannot be excluded. The decrease in FE_{Na} and FE_{Cl} in response to indomethacin is likely to be attributable to the decrease in PGs synthesis since prostaglandin E_2 and prostacyclin have been shown to act directly on renal tubules and produce natriuresis.[27] PGE_2 also inhibits chloride reabsorption.[28] The increase in FE_{Na} and FE_{Cl} in response to enalapril is the result of reductions in aldosterone secretion secondary to the decreased AII. FE_{Na} and FE_{Cl} are further increased upon intrarenal arterial injection of RVV and may reflect the direct tubular effects. This finding is confirmed by a previous report on an isolated perfused triturus kidney in which the venom decreased the potential defference across the proximal tubular membrane.[29] In summary, when RVV was injected into the renal artery, the local renal vasodilatating effect, mediated by prostaglandins, predominated and blunted renal autoregulation. Indomethacin inhibited not only the hypotensive effect of the RVV but it also inhibited

the local renal vasodilatation. Enalapril could not maintain the RBF when prostaglandin synthesis was inhibited. Whether RVV decreased the PRA, indicating the angiotensin converting enzyme activity presented in the RVV composition remains to be studied.

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