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5/6 부분신절제 백서모델에서 Angiotensin Converting Enzyme Inhibitor(ACEI) 및 Angiotensin II AT1 수용체길항제(AT1 RA)가 Plasma Renin Activity 및 Angiotensin II level 에 미치는 영향

충남의대 내과학교실, 병리학교실*: 김종학, 나기량, 황평주, 서광선*, 이강욱, 신영태

5/6 부분신절제 백서모델은 전형적인 만성신부전증모델로 신장손상 매카니즘에 renin-angiotensin system (이하 RAS)이 중요한 역할을 담당할 것으로 추정되며 이러한 모델에서 RAS 억제는 신조직손상 진행을 억제한다는 보고들이 있다. RAS 억제 방법으로 ACEI 는 angiotensin I 이 angiotensin II (이하 A II)로의 전환을 차단하고 AT1 RA 는 AII 의 작용을 AT1 수용체 단계에서 억제하기 때문에 서로 RAS 억제 단계가 다르다. 따라서 두가지 치료방법들은 혈중 plasma renin activity(이하 PRA) 및 A II 치에 각각 다른 영향을 미칠 것으로 생각된다. 저자들은 이러한 모델에서 ACEI 나 AT1 RA 의 장기적인 치료가 수축기혈압, PRA 및 A II 농도에 어떠한 영향을 미치는지 알아보고자 본 연구를 수행하였다.

체중 270-300 g 의 웅성 Sprague Dawley 백서를 thiopental sodium 마취(50 mg/kg)하에 우측 신장을 절제하고 좌측 신동맥 분지 2-3 개를 결찰하는 방법으로 5/6 부분신절제술을 시행하였다. 대상동물들은 각각 정상대조군, 5/6 부분신절제 대조군, 5/6 부분신절제 ACEI 치료군(enalapril, 100 mg/ L in drinking water), 5/6 부분신절제 AT1 RA 치료군 (losartan, 250 mg/ L in drinking water)으로 구분였으며 치료기간은 모두 3 개월이었다.

수축기혈압은 3 개월째 5/6 부분신절제 대조군 165 ± 23 mmHg(이하 M ± SD)에 비하여 ACEI 치료군 132 ± 9 mmHg, AT1 RA 치료군 124 ± 7 mmHg 로 양군 모두 의미있게 낮았다(각각 $p < 0.05$, $p < 0.01$). PRA 는 각각 ACEI 치료군 7.2 ± 2.9 ng/ml/hr, AT1 RA 치료군 4.7 ± 0.4 ng/ml/hr, 5/6 부분신절제 대조군 2.7 ± 1.1 ng/ml/hr, 정상대조군 2.7 ± 1.4 ng/ml/hr 이었으며 정상대조군과 5/6 부분신절제 대조군 사이에 의미있는 차이는 없었다 ($p > 0.05$). 그러나 정상대조군 및 5/6 부분신절제 대조군에 비하여 ACEI 치료군 및 AT1 RA 치료군에서는 모두 의미있게 높았다($p< 0.05$, $p < 0.05$). ACEI 치료군과 AT1 RA 치료군사이에 의미있는 차이는 없었다($p > 0.05$). Plasma A II 치는 AT1 RA 치료군이 1938 ± 435 pg/ml 으로 정상대조군 484 ± 294 pg/ml 에 비하여 의미있게 높았다($p < 0.01$).

이상에서 연구자들은 5/6 부분신절제 백서모델에서 3 개월간 ACEI 및 AT1 RA 치료는 대조군에 비하여 혈압을 정상화시키며 모두 PRA 를 상승시키지만 혈중 AII 농도는 AT1 RA 사용시에 의미있게 증가함을 확인하였다.

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Role of the Nitric Oxide in the Erythropoietin-induced Hypertension

Ki Chul Choi, M.D., Kwon Jung, M.D., Seong Cheol Lee, M.D., Soo Wan Kim, M.D., Nam Ho Kim, M.D., Jong-un Lee, M.D.*, and Young Joon Kang, M.D.

Department of Internal Medicine and Physiology*, Chonnam University Medical School, Kwangju, Korea

Objectives : Hypertension is a common complication of recombinant human erythropoietin (rHuEpo) therapy. However, the mechanism of the rHuEpo-induced hypertension is uncertain. The present study was aimed to determine if the role of endogenous L-arginine-NO pathway on the rHuEpo-induced hypertension in chronic renal failure (CRF).

Methods : We examined the effects of rHuEpo and vehicle alone on nitric oxide system in 5/6 nephrectomized rats (Sprague-Dawley males weighing 200-250 g), and compared those with control rats. After 5/6 nephrectomy operation, animals were observed for 6 weeks to allow full expression of CRF anemia, and then they were treated with rHuEpo (200 U/kg s.c. twice per week) or vehicle alone for another 6 weeks. On the experimental day, under thiopental anesthesia (50 mg/kg, i.p.), the right femoral artery was cannulated to measure arterial pressure. Blood was collected from the trunk for the determination of creatinine, hematocrit and NOx (NO_2^- and NO_3^-) concentrations. Urine samples were collected for the determination of NOx. Abdominal aortas and kidneys were rapidly removed, immediatedly frozen for the determination of tissue NOx and Western blot analysis of nitric oxide synthase (NOS). Thoracic aortas were isolated from rats and their changes in isometric tension in response to acetylcholine and nitroprusside were examined.

Results : After 6 weeks of rHuEpo treatment there was a significant increase in mean arterial pressure (165±6 mmHg vs 147±11 mmHg, $p<0.05$) and hematocrit (41.6±2.9 % vs 34.9±0.9 %, $p<0.05$) compared with 5/6 nephrectomized rats with vehicle alone. Plasma and kidney NOx levels were not significantly different among three groups. However, urine NOx levels were significantly lower in 5/6 nephrectomized rats with or without rHuEpo treatment compared with controls (644±124 μM, 689±139 μM vs 1437±236 μM, respectively, $p<0.01$). The endothelial NOS (ecNOS) proteins were expressed lower in the kidney and aorta of 5/6 nephrectomized rats with or without rHuEpo treatment compared with controls. However, there was no significant difference of ecNOS protein expression in the kidney and aorta between the two 5/6 nephrectomized groups. The inducible NOS (iNOS) proteins in the kidney and aorta were not significantly different among three groups. Acetylcholine and nitroprusside induced dose dependent relaxation of phenylephrine-precontracted (3.5×10^{-6} mol/L) aortic rings in uremic rats, respectively. However, their degrees were not different between 5/6 nephrectomized rats with rHuEpo therapy and with vehicle alone.

Conclusion : These results indicate that rHuEpo induced or aggrevated hypertension in 5/6 nephrctomized rats. However, nitric oxide system did not play a role on the erythropoietin-induced hypertension.