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**20-HETE AND RENAL VASOCONSTRICTOR RESPONSIVENESS**

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20-HETE is a cytochrome P450-derived constrictor eicosanoid produced by preglomerular microvessels thereby, regulating glomerular hemodynamics. Removal of the tonic inhibitory influence of nitric oxide (NO) has been reported to increase renal 20-HETE release. As inhibition of NO synthesis enhances responses to vasoconstrictor agents, we examined a contribution via increased 20-HETE generation. In the rat kidney perfused with Krebs' buffer containing indomethacin (5.6 μM), responses to U46619, a thromboxane mimetic, were compared before and after nitroarginine (L-NA) to inhibit NOS. L-NA (100 μM) raised perfusion pressure (PP) from 79±3 mmHg to 190±7 mmHg and enhanced constrictor responses to U46619. Thus, 10, 30, 100 and 300 ng U46619 increased PP by 7±1, 17±2, 50±7 and 67±7 mmHg, respectively, before L-NA and 15±1, 37±7, 68±10, and 85±11 mmHg after L-NA (n=5–10) which did not increase 20-HETE efflux from the kidney, 2.4±1.73 ng/min. versus 3.45±1.20 ng/min. before L-NA. Nonetheless, an inhibitor of ω-hydroxylase, DDMS (n=5), reduced 20-HETE release from 2.87±0.97 ng/min. to 1.49±0.34 ng/min. and normalized the enhanced responsiveness to U46619. When PP was elevated with phenylephrine to the same level as that induced by L-NA, vasoconstrictor responses to U46619 were enhanced to a similar degree as that seen with L-NA, an effect that was also prevented by DDMS. Similarly, DDMS reduced responses in the absence of elevation of PP. We suggest that 20-HETE plays a facilitatory role in vasoconstrictor responses, possibly by influencing the activity of K channels, rather than increased generation following NOS inhibition directly contributing to enhanced vasoconstrictor responsiveness. Thus, charybotoxin, an inhibitor of large conductance, calcium-activated K channels, the target of 20-HETE, also enhanced renal vasoconstrictor responses to U46619 whereas apamin, an inhibitor of small conductance, calcium-activated K channels was without effect.

Key Words: Renal, Vasoconstrictor Responses, 20-HETE

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**CARDIOVASCULAR REACTIVITY AND ANGIOTENSIN II RECEPTOR GENE EXPRESSION IN 5/6 NEPHRECTOMISED RATS: THE EFFECT OF HUMAN EPOETIN TREATMENT**

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According to previous results the recombinant human erythropoietin (rHuEpo) treatment increases the blood pressure (BP) in rats and improves the pressor response to norepinephrin (NE) in uremic patients. The aim of our study was to examine the vascular reactivity of the rHuEpo on BP and peripheral vascular resistant (PVR). The relative abundance of angiotensin II (ang II) receptor (AT1-R) mRNA was examined in mesenteric arterial blood vessels of rats treated with erythropoietin and matched controls.

In the first group of male Wistar rats 5/6 nephrectomy (5/6X) was performed, the second group was only sham-operated. 15 E/100g of rHuEpo was administrated i.p. twice weekly for 20 weeks in the half of both groups. At the end of the 20-weeks, the mean arterial pressure (MAP) was measured in anesthetized animals with a Statham pressure transducer. 10 or 20 ng/100 g NE and 1 or 2 ng/100 g ANG II were administered i.v. The mesenteric blood flow (MBF) was detected with a Transonic Transit Time Flowmeter T206, from which the PVR was calculated. The pressor response was calculated as a percentage of the MAP increase. Semi-quantitative and quantitative reverse transcription PCR (RT-PCR) amplification was examined of the mesenteric blood vessels. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as a standard for quantification.

The pressor response was significantly higher to both NE (50.1±7.6 and 63.1±6.9) and ANG II (56.6±14.8 and 61.1±14.1) at all doses in the 5/6X rats. The MBF also increases for NE (46.4±12.0 and 53.9±17.8; p<0.01), but there was no reaction for ANG II. In group 5/6X the MAP also increases (120.0±7.2 mmHg) for rHuEpo treatment, but it was an amazing that the pressor has not changed to NE nor ANG II. It is unexpected, because in ANG II as compared to the not treated animals. An increase of AT1-R mRNA was demonstrated in treated animals.

Semi-quantitative RT-PCR showed an average 1.95 fold increase, although this difference was not statistically significant. With quantitative RT-PCR an average 2.51 fold increased expression of angiotensin II receptor could be detected.

The data suggest that the pressor response to NE and ANG II in the 5/6X rats were increased. The positive effect of erythropoietin on expression of angiotensin II receptors in blood vessels suggests a possible explanation for hypertension during long-term erythropoietin treatment caused by the increased activity of the rennin-angiotensin system (local) in 5/6X rats.

Key Words: Erythropoietin, Cardiovascular Reactivity, Pressure Response

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**ANTIHYPERTENSIVE EFFECTS OF OMAPATRILAT ON THE CIRCULATING AND RENAL ANGIOTENSIN SYSTEM**

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Because Omapatrilat (OMA), a new vasopeptidase inhibitor, inhibits the activity of ACE and neutral endopeptidase 24.11 (NEP), we investigated in SHR (BW: 0.42 kg) its effect on plasma and urinary concentrations of angiotensin (Ang) I, Ang II and Ang-(1-7) during 17 days of administration of either the drug (n=15, 10 mg/kg/d) or vehicle (n=14) in the drinking water. OMA induced a sustained lowering of systolic blood pressure (-68 mm Hg) without changes in cardiac rate. The mild positive water balance produced by OMA did not cause natriuresis or kaliuresis. Blood pressure normalization was accompanied with increases in plasma Ang I (2,700%), Ang II (131%), and Ang-(1-7) (163%) levels, paralleling pronounced increases in urinary excretion rates of Ang-(1-7) corrected for creatinine. Increases in plasma and urine Ang-(1-7) confirms that both ACE and NEP