The role of endothelin in immune-mediated vascular injury

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Hypertension is common and in the majority of cases its cause remains unknown. Recent interest has focused on the role of macrophages (M Φ) in blood pressure (BP) regulation. Endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor mediating its effects through two receptors - the endothelin-A receptor (ET_A) and endothelin-B (ET_B) receptor. The ET_B receptor has a specific role in ET-1 clearance. We investigated the role of the M Φ ET_B receptor in a model of angiotensin II (Ang II)-mediated end-organ damage.

M Φ ET_B receptor deficient mice (*LysMET_B^{-/-}*) and controls were exposed to Ang II infusion for 6 weeks under a high salt diet. We assessed BP *via* telemetry, cardiac structure and function and endothelial function by Doppler ultrasound, end-organ injury and plasma and urine ET-1.

At baseline, components of BP did not differ between groups and increased similarly with Ang II. Whereas after 6 weeks of Ang II *LysMET_B^{-/-}* and controls had similar left ventricular hypertrophy and cardiac insufficiency, endothelial function was better in *LysMET_B^{-/-}* at both baseline and after Ang II (% dilation of basilar artery in response to CO₂, *LysMET_B^{-/-}* vs. controls: baseline: 20 vs. 11%, $p < 0.01$; at 6 weeks: 11 vs. 0%, $p < 0.01$). Baseline renal function and proteinuria did not differ between groups. After Ang II, *LysMET_B^{-/-}* showed similar renal function compared to controls but less proteinuria (urine albumin:creat, mg/mmol: 208 $\pm$ 10 vs. 530 $\pm$ 25, $p < 0.01$), glomerulosclerosis (34 $\pm$ 2 vs. 61 $\pm$ 4%, $p < 0.001$), and fewer renal M Φ compared to controls (F4/80 staining *per* high power field, *LysMET_B^{-/-}* vs. controls: 1.1 $\pm$ 0.7 vs. 3.2 $\pm$ 0.5%, $p = 0.02$), although similar levels of CD3⁺ T cells. Plasma ET-1 was no different at baseline but increased more in *LysMET_B^{-/-}* with Ang II (*LysMET_B^{-/-}* vs. controls after 6 weeks Ang II: 3.7 $\pm$ 0.7 vs. 1.4 $\pm$ 0.2 pg/ml, $p = 0.03$). Urine ET-1 was similar baseline and 6 weeks.

Deletion of the M Φ ET_BR is associated with a blunting of the effects of systemic Ang II infusion as reflected by less endothelial dysfunction, reduced inflammation and end-organ damage. The mechanisms for these effects are the focus of ongoing research.