## Chemokine receptors as novel pharmacological targets to reduce blood pressure during experimental hypertension in mice

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**Introduction:** Leukocyte infiltration into the artery wall plays a pathophysiological role in hypertension by promoting vascular inflammation and endothelial dysfunction (Guzik *et al.*, 2007). Chemokines are chemoattractant cytokines that bind to receptors expressed on leukocytes and thereby promote their migration into tissues.

**Aims:** To identify chemokine receptors that are upregulated in the vascular wall during deoxycorticosterone acetate (DOCA)/salt-induced hypertension in mice and to evaluate the impact of pharmacological inhibition of these receptors on systolic BP.

**Methods:** Hypertension was induced in C57Bl6/J mice by DOCA/salt treatment as previously described (Guzik *et al.*, 2007). Some DOCA/salt-treated animals received daily i.p. injections of either the CCR2 antagonist, INCB3344 (30 mg/kg/d) or vehicle (10% DMSO/0.9% carboxymethylcellulose) from days 10-21. Systolic BP was monitored by tail cuff and aortas were removed after 21 d for measurement of chemokine receptor expression by real-time RT-PCR.

**Results:** DOCA/salt-treated mice had markedly higher systolic BP (158±2 mmHg) than sham-treated animals (114±5 mmHg; $P<0.0001$; n11). A preliminary RT-PCR screen of a gene panel containing 20 chemokine receptors indicated an increase in mRNA expression of CCR2 in aortas from DOCA/salt-treated mice (n=3). Taqman® real-time PCR confirmed this increase in CCR2 expression (by 2.2-fold), and also revealed elevated expression of the CCR2 ligands CCL2 (2.3-fold), CCL7 (4.0-fold), CCL8 (2.8-fold) and CCL12 (4.2-fold) in DOCA/salt-treated mice (n=7 for all genes; $P<0.05$). INCB3344-treatment blunted DOCA/salt-induced increases in aortic expression of CCR2 and CCL2 by 55% and 45%, respectively (n=6-8, $P<0.05$) but did not alter CCL7, CCL8 and CCL12 levels. DOCA/salt-induced elevations in systolic BP were also reversed by INCB3344 (by 15 mmHg; n=11, $P<0.01$) whereas the vehicle had no effect (n=10).

**Discussion:** Thus CCR2 represents a promising therapeutic target to reduce BP in hypertension. Future studies will examine if the anti-hypertensive effects of INCB3344 involve inhibition of pro-inflammatory leukocyte migration into the vascular wall.

Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG. (2007) *Journal of Experimantal Medicine* **204:** 2449-2460.