**Interleukin-18 signals via a non-canonical short IL-18 pathway during deoxycorticosterone/salt-induced hypertension**

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Introduction. The pro-inflammatory cytokine, interleukin-18 (IL-18), is elevated in patients with hypertension and chronic kidney disease. We have reported that genetic ablation of IL-18 prevents the development of experimental hypertension and renal inflammation. IL-18 signals via the IL-18 receptor that requires recruitment of the IL-18 receptor accessory protein (IL-18RAP) for canonical signalling. However, it was recently discovered that a truncated ‘*short*’ IL-18 fragment, can activate downstream inflammation via an alternative interferon-stimulated gene-15 (ISG15) pathway.

Aim. To determine whether IL-18 drives deoxycorticosterone acetate (DOCA)/salt-induced hypertension and renal inflammation via its canonical receptor complex.

Methods. Male and female wild type (WT), *Il18*-/- and *Il18rap*-/- mice (n=10-12) were anaesthetised (5% isoflurane) and subjected to uninephrectomy. Mice were randomly assigned to receive either DOCA (2.4 mg/d, *s.c.* pellet) with high salt (0.9% in drinking water), or placebowith normal drinking water for 21 days. Systolic blood pressure (SBP) was measured weekly (tail-cuff plethysmography). At endpoint, the remaining kidney (right) was harvested to assess renal immune cell accumulation (flow cytometry) and renal inflammatory gene expression, including *Isg15* (qPCR).

Results. Baseline SBP was similar across sexes and genotypes (WT: 131±2 mmHg; *Il18*-/-: 131±3 mmHg*; Il18rap*-/-: 133±2 mmHg). In WT mice, DOCA/salt caused an increase in SBP compared to placebo controls (161±3 mmHg; *P*<0.05). Consistent with previous findings, *Il18*-/- mice exhibited a blunted pressor response to DOCA/salt (147±5 mmHg; *P*<0.05 vs WT). In contrast, *Il18rap*-/- mice were not protected from DOCA/salt-induced hypertension (167±3 mmHg) or renal leukocyte (CD45+) accumulation. In both male and female WT mice, DOCA/salt-treatment caused a >2-fold increase in renal *Isg15* mRNA expression, which was completely abolished in *Il18*-/- mice, but unchanged in *Il18rap*-/- mice.

Discussion. *Il18rap* deficiency does not protect against DOCA/salt-induced hypertension and renal inflammation, suggesting that IL-18 may act via a non-canonical ISG15-dependent pathway to drive DOCA/salt-induced hypertension.

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