G protein-coupled estrogen receptors: novel therapeutic targets in aldosterone-induced hypertension?

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Introduction. Some effects of aldosterone may be modulated by the G protein-coupled estrogen receptor 1 (GPER). Furthermore, the GPER agonist, G-1, can exert T cell-mediated anti-inflammatory actions, acutely lower blood pressure (BP), and reduce post-stroke infarct injury.

Methods. Here we tested in mice the effects of G-1 (0.03 mg/kg/d s.c.) and G-15 (GPER antagonist; 0.3 mg/kg/d s.c.) on BP (using tail-cuff plethysmography) over 14 d in two models of hypertension: 1) aldosterone/salt (0.72 mg/kg/d s.c. + 0.9 % NaCl for drinking) and 2) angiotensin II (0.7 mg/kg/d s.c.); and also assessed sex differences, and the role of lymphocytes and endogenous estrogen (in ovariectomised females) in those effects. All groups were n=8 or more.

Results. In male C57Bl6 mice, the aldosterone/salt-induced increase in BP (~25 mmHg) was attenuated by ~50 % with co-administration of G-1 ($P<0.05$). G-15 did not alter aldosterone/salt-induced hypertension in male C57Bl6 but prevented the anti-hypertensive effect of G-1. Moreover, whereas aldosterone/salt alone had no effect on BP in female C57Bl6 mice for >7 d, co-administration of G-15 with aldosterone/salt resulted in a prompt increase of ~20 mmHg by d 7 ($P<0.05$). In contrast, ovariectomised females resembled males in their BP profile in response to aldosterone/salt. There was virtually no effect of aldosterone/salt on BP in either male or female RAG1-deficient (RAG KO) mice, but this could be rescued by adoptive transfer of T cells from C57Bl6 into RAG KO ($P<0.05$). Neither G-1 nor G-15 had any effect on angiotensin II-induced hypertension in male C57Bl6 mice. T cells, as well as B cells, macrophages and neutrophils in spleen and kidneys were found to have high expression of GPER.

Conclusion. The findings suggest that aldosterone/salt-induced hypertension is strictly T lymphocyte-dependent and is markedly suppressed by GPER activation on these cells by endogenous estrogen or by administration of G-1.