Objective: Inflammation is the underlying cause of vascular dysfunction in many cardiovascular diseases (CVD). We have previously shown that the capsaicin receptor, transient receptor potential vanilloid 1 (TRPV1), located on perivascular C-fibre nerve-endings, is involved in the regulation of pressure-induced myogenic tone. We have postulated that the arachidonic acid metabolite, 20-hydroxyeicosatetraenoic acid (20-HETE), is an endogenous ligand that stimulates TRPV1. The aim of this study was to investigate the role of TRPV1 in the inflammatory-mediated regulation of myogenic tone.

Methods: Small mesenteric arteries (<150 μm diameter) from wild-type (WT) and TRPV1 knockout (KO) mice were mounted on a perfusion myograph and pressure-diameter curves (20-100 mmHg) were determined in the absence, and then in the presence, of the inflammogens phorbol 12-myristate 13 acetate (PMA; PKC activator; 10 nM) or prostaglandin E2 (PGE2; PKA activator, 100 nM), or the PKA inhibitor, H89 (2 μM). A final curve was constructed in the absence of extracellular calcium+EGTA (2 mM) to determine the passive pressure-diameter response. Changes in mean arterial pressure (MAP) were determined in response to bolus doses of 20-HETE (1.4–42 nmoles i.v.) in conscious male and female WT and KO mice.

Results: In arteries of male WT mice PMA treatment enhanced myogenic tone by 37.4±6.3 % (p<0.01, n=6); an effect suppressed in arteries of male KO mice (17.6±4.6 % increase, n=7, p<0.001). PMA treatment enhanced myogenic tone by a similar amount in arteries of both WT (34.3±4.0 %) and KO females (24.4±5.0%, n=4). In addition, PGE2 treatment enhanced (p<0.01, n=5) and H89 (p=0.02, n=6) suppressed myogenic tone in arteries of male WT mice. These drugs had no effect on the arteries of male KO mice (n=6), nor on arteries of WT or KO females (n=6). 20-HETE caused an elevation of MAP in male WT mice (max. 16±1 mmHg, n=5). This elevation was substantially lower in KO males (max. 4±2 mmHg, n=4, p<0.001). In female mice, 20-HETE caused similar elevations of MAP in both WT (max. 8±2 mmHg, n=6) and KO (max. 12±1 mmHg, n=5) mice, and the increase in MAP was lower in WT females compared with males (p<0.01).

Conclusions: Inflammatory mediators enhance myogenic tone in resistance arteries. The myogenic response is increased after PGE2 incubation in arteries of male, but not female mice, and appears to be due to PKA-dependent modulation of TRPV1 activity. 20-HETE causes elevations of MAP in male mice that are dependent upon TRPV1 activation, whilst no role for TRPV1 was evident in females. Together these results suggest a sex difference in the regulation of myogenic tone and MAP and highlight a novel pathway centred on TRPV1 activation that might underlie the enhanced susceptibility to vascular dysfunction and CVD in males.

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