Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol12Issue3abst135P.pdf

Deletion Of The Ion Channel TRPV4 Is Not Protective In A Mouse Model Of Sepsis

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Sepsis is a systemic inflammatory response syndrome triggered by microbial infection that can progress to septic shock, encompassing cardiovascular collapse, insufficient tissue perfusion and multi-organ failure (1). There is increasing evidence that Transient Receptor Potential (TRP) ion channels can modulate vascular function. The cation channel TRP Vanilloid 4 (TRPV4) is expressed in vascular endothelium and causes vasodilatation through stimulation of nitric oxide release or direct hyperpolarisation of vascular smooth muscle (2). Excessive TRPV4 activation leads to profound hypotension and circulatory collapse – both key features of sepsis pathogenesis (3). Based on our observation of endotoxin-induced sensitisation of TRPV4 activity in vascular cells, we hypothesised that loss of TRPV4 signaling would be protective against cardiovascular dysfunction in a mouse model of sepsis (endotoxaemia).

Multi-parameter monitoring of conscious systemic haemodynamics (following radiotelemetry probe implantation), mesenteric microvascular blood flow (laser speckle contrast imaging) and blood biochemistry (iSTAT blood gas analysis) was carried out in male wild type ($^{+/+}$) or TRPV4 knockout ($^{-/-}$) C57Bl/6 mice (25-30 g). Baseline haemodynamics were recorded over 2 weeks after which endotoxaemia was induced by a single intravenous injection of lipopolysaccharide (LPS; 12 mg/kg) and systemic haemodynamics monitored for up to 24 hrs. Blood flow recording was then conducted under terminal anaesthesia after which a terminal inferior vena cava bleed was obtained for haematological/biochemical analysis. All procedures were carried out under isoflurane (2%) anaesthesia.

No significant differences were observed in baseline haemodynamics or mesenteric blood flow, although TRPV4$^{-/-}$ mice exhibited a trend towards hypotension, relative to TRPV4$^{+/+}$ littermates. Naïve TRPV4$^{-/-}$ mice were also significantly acidotic relative to $^{+/+}$ counterparts (blood pH: 7.19 ± 0.03 vs. 7.31 ± 0.01, respectively; $p<0.05$, 1-way ANOVA + Bonferroni post-hoc test, n=9). Following induction of sepsis, all mice became significantly hypotensive, though there was no significant difference in the degree of hypotension between TRPV4$^{-/-}$ and TRPV4$^{+/+}$ mice [Δmean arterial pressure (95% CI): -13.08 mmHg (-24.07 to -2.09) vs. -12.95 mmHg (-25.23 to +0.66), respectively, ns]. TRPV4$^{-/-}$ mice exhibited a higher sepsis severity score (assigned in a blinded manner based on posture, mobility, gait, piloerection and aversion to touch; $p<0.05$, 1-way ANOVA + Bonferroni post-hoc test) as well as a trend towards exaggerated hypothermia relative to TRPV4$^{+/+}$ counterparts. While septic TRPV4$^{+/+}$ mice became significantly hypernatraemic relative to the naïve state (155.9 ± 0.9 mM vs. 150.3 ± 1.7 mM, respectively), this was not observed in septic TRPV4$^{-/-}$ mice (150.6 ± 1.0 mM vs. 150.2 ± 0.9 mM). Mesenteric blood flow was inhibited by topical application of the TRPV4 agonist GSK1016790A (1µM; -7.6 ± 1.3%) in naïve TRPV4$^{+/+}$ mice, but enhanced 24 hr following LPS injection (+12.1 ± 6.2%).

Contrary to the initial hypothesis, loss of TRPV4 signaling did not attenuate sepsis-induced cardiovascular dysfunction: in fact, pathology appeared to be modestly exaggerated in mice lacking TRPV4. The contribution of TRPV4 to numerous physiological processes (vascular endothelial and smooth muscle regulation; osmoregulation; thermoregulation and immunoregulation) complicates the interpretation of this data. Local targetting of TRPV4 signalling may be more beneficial in sepsis treatment than global inhibition.

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