Physiology and pharmacology Piezo1 channels

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The sensing of physical forces arising because of blood flow and other factors is critical for the maturation, reactivity and remodelling of blood vessels which are required in embryonic development and adult life, yet the mechanisms by which the physical forces are sensed have been elusive. It has been unclear if there are specific force sensing proteins and how they might sense force and generate appropriate downstream signals. We have revealed how Ca^{2+} -permeable non-selective cationic channels formed by assembly of Piezo1 proteins act as sensors of physiological force and determinants of vascular structure and responsiveness in both development and adult physiology (Li et al 2014 Nature 515, 279-; Rode et al 2017 Nature Communications 8, 350-). Global and endothelial-specific disruption of mouse Piezo1 profoundly disturbed the developing vasculature and was embryonic lethal within days of the heart beating. The importance of Piezo1 channels as sensors of blood flow was shown by the Piezo1 dependence of shear stress-evoked ionic current and Ca^{2+} influx in endothelial cells and the ability of exogenous Piezo1 to confer sensitivity to shear stress on otherwise resistant cells. Downstream of this Ca^{2+} influx there was protease activation and spatial reorganization of endothelial cells to the polarity of the applied force. We then generated conditional deletion of Piezo1 in endothelial cells of the adult mouse. We found that elevated blood pressure of whole body physical exercise depended on endothelial Piezo1. The mechanism was a vascular bed-specific effect of Piezo1 which opposed endothelium-dependent relaxation mediated by endothelium-dependent hyperpolarization which led to vasoconstriction when fluid flow was elevated. We concluded that endothelial Piezo1 has a role as an exercise sensor. Intriguingly, a small-molecule called Yoda1 could mimic the effect of fluid flow, suggesting the possibility to induce or enhance this effect of exercise by using a pharmacological agent. These findings and other new data will be presented and discussed. All experiments were performed according to UK legal and ethical requirements. The research was supported by grants from the Medical Research Council UK, Wellcome Trust and British Heart Foundation.